Transition-Metal-Catalyzed Addition of Heteroatom−Hydrogen Bonds to Alkynes

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1. Introduction

The addition of heteroatom−hydrogen (Het−H) bonds across the carbon−carbon triple bond, catalyzed by transition-metal complexes, is one of the most interesting and intriguing subjects in organic chemistry.[1] It includes such different types of bonds as N−H, O−H, S−H, Se−H, and P−H, where the nature of the hydrogen atom can be completely different depending on the electronegativity of the heteroatom, its oxidation state [for example, R_2P-H and $(RO)_2(O)P-H$ or RO−H and RC(O)O−H], and the nature of the organic group R. Certainly, it is possible to expect the influence of the electronic effects in the alkyne, i.e., the presence of strong electron-withdrawing or strong electron-donating groups. Of course, the nature of the transition-metal complex also plays a key role in the reaction.

All these processes are very important from the synthetic point of view because, in principle, the addition reactions can be performed with 100% atom efficiency, without any waste formation, and for this reason they fulfill the requirements of green chemistry better than substitution reactions leading to the same products. As a result of these reactions, many very important and useful alkenyl organic compounds, such as phosphines, phosphonates, sulfides, selenides, and different nitrogen- and oxygen-containing products, can be obtained. Furthermore, the intramolecular version of this reaction (the heteroannulation reaction) is one of the best and straightforward ways to obtain nitrogen- and oxygen-containing heterocycles.

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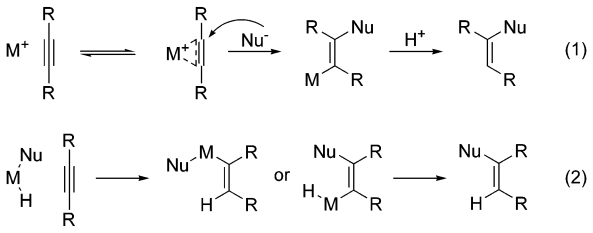
Francisco Alonso (right) was born in Villena (Alicante) in 1963. He received his B.Sc. (1986), M.Sc. (1988), and Ph.D. (1991) degrees in Chemistry from the University of Alicante. After a postdoctoral stay (1992–1994) as a Fleming fellow at the University of Oxford, U.K., with Professor S. G. Davies, he moved back to the University of Alicante and joined the research group of Professor M. Yus. He became Associate Professor in 1998, and his research interest has focused on the development of new synthetic methodologies involving active metals and the application of organometallic intermediates to the synthesis of naturally occurring molecular structures. He was awarded with the Ph.D. Extraordinary Prize in 1992.

Irina Beletskaya (middle) received her Diploma degree in 1955, her Ph.D. degree in 1958, and her Doctor of Chemistry degree in 1963 from Moscow State University. The subject for the latter was Electrophilic Substitution at Saturated Carbon. She became a Full Professor in 1970 and in 1974 a Corresponding Member of the Academy of Sciences (USSR), of which she became a full member (Academician) in 1992. She is currently Head of the Laboratory of Organoelement Compounds, Department of Chemistry, Moscow State University. Irina Beletskaya is Chief Editor of the *Russian Journal of Organic Chemistry*. She was President of the Organic Chemistry Division of IUPAC from 1989 to 1991. She was a recipient of the Lomonosov Prize (1979), the Mendeleev Prize (1982), and the Nesmeyanov Prize (1991). She is the author of more than 500 articles and 4 monographs. Her current scientific interests are focused on (i) transition-metal catalysis in organic synthesis, (ii) organic derivatives of lanthanides, and (iii) carbanions and nucleophilic aromatic substitution.

Miguel Yus (left) was born in Zaragoza in 1947. He received his B.Sc. (1969), M.Sc. (1971), and Ph.D. (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to the University of Oviedo, where he became Associate Professor in 1977, being promoted to Full Professor in 1987 at the same university. In 1988 became Chair in Organic Chemistry at the University of Alicante, where he is currently Head of the Organic Chemistry Department. Professor Yus has been a visiting professor at different institutions such as ETH-Zürich and the Universities of Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, and Paris VI. He is a member or fellow of the chemical societies of Argentina, England, Germany, Japan, Spain, Switzerland, and the United States. He is a coauthor of more than 300 papers mainly in the field of the development of new methodologies involving organometallic intermediates in synthetic organic chemistry. Among others, he has recently received the Spanish–French Prize (1999), the Japan Society for the Promotion of Science Prize (2000), and the Stiefvater Memorial Lectureship Award (2001).

In comparison with other addition reactions, such as radical reactions or those catalyzed by acids and bases, these reactions proceed, as a rule, under much milder conditions, giving higher yields of the products, and what it is the most important, they proceed with good or excellent regio- and stereoselectivities. Without any doubt, this approach to the synthesis of many useful biologically active compounds, building blocks, new materials, monomers, and fine chemicals, among others, has great potential, particularly because the starting materials are relatively readily available and cheap.

Scheme 1



The main problem that everyone has to face in these reactions (also in industrial applications) is to find the proper catalyst, which should be not only efficient but relatively cheap and stable. In general, they suffer from short lifetimes, low TON and TOF, and limited reaction scope. This still remains a big problem, particularly combined with our poor understanding of the mechanisms involved in these reactions. These mechanisms can be quite different depending on the Het−H bond taking part in the reaction, but they are also different within the same type of Het−H bond for the diverse catalysts used. This behavior is exemplified by the two different mechanisms that explain the hydroamination of alkynes catalyzed by titanium and palladium.

By opening a textbook on organometallic chemistry or organometallic catalysis, one can see that the activation of the carbon−carbon triple bond toward nucleophilic attack can be performed by metals with high Lewis acidity (alkyne activation) [Scheme 1, eq 1]. It is also easy to realize that as a result of the *anti*-addition of the nucleophile, the product should be obtained with *trans*-stereochemistry. However, in many other cases the picture is quite different, the reactions proceeding as a result of the insertion of the alkyne moiety into M−H or M−Nu bonds of "H−M−Nu" complexes, typically with *syn*-addition (nucleophile activation) [Scheme 1, eq 2].

To analyze the state of art of this important field, we decided to consider all these reactions not only from the point of view of their application, but mainly from a mechanistic point of view, using the known data to carry out a comparative study for the different type of reactions. Many (if not the majority) of these reactions have been tackled in excellent reviews (see the introduction to every part of the review). However, some of them are too general, covering not only alkynes as substrates but also other carbon−carbon multiple bond systems, together with other type of additions such as hydrogenation, hydroformylation, hydrocarbonylation, hydrocarbonation, etc. In those reviews dedicated to the formation of a particular bond, C−N, C−S, C−P, etc., the authors also considered the reaction of addition to alkynes together with other addition processes which may have another character, whereas an attempt to compare the different types of Het−H bond additions has never been undertaken.

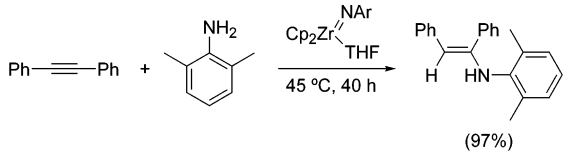
2. Hydroamination

Hydroamination of alkynes is a fundamental reaction in organic chemistry which allows, in a straightforward manner, the preparation of valuable nitrogen-containing compounds such as enamines and imines, among others. A variety of both catalytic and noncatalytic methods have appeared in the literature to overcome the high activation energy required for this process. For instance, Cossy et al. reported the simple thermal- and acid-promoted cyclization of aminoalkynes, the main drawbacks of this methodology being the elevated temperatures required (150−210 °C) and the need of having a phenyl acetylene moiety in the starting structure.[2] Anionic cyclization by treatment of aminoalkynes with *n*-BuLi or $LiAlH_4$ was also a facile and mild method but limited to the presence of a phenylacetylene moiety.[3] Jacobi et al. found that excess of TBAF followed by thermal treatment allowed the intramolecular cyclization of amido pyrroloalkynes as specific substrates.[4] An interesting method for activating the triple carbon−carbon bond was described by Trost et al., involving the use of phosphines and applied to the intermolecular α-addition of nitrogen nucleophiles (with an electron-withdrawing group attached to nitrogen) to conjugated alkynoates.[5] A remarkable contribution to this field was made by Knochel et al., reporting the $CsOH·H_2O$-catalyzed intermolecular addition of anilines and heterocyclic amines to phenylacetylene at temperatures of 90−120 °C.[6] Metallic salts and oxides were used very early in the past century to promote mainly the addition of ammonia or simple amines to acetylene, thus obtaining valuable nitrogen-containing products from an industrial point of view.[7] Other metallic salts such as $HgCl_2$, $Hg(OAc)_2$, or $Tl(OAc)_3$ were studied by Barluenga et al. in the catalytic and noncatalytic addition of primary and secondary aromatic and aliphatic amines to terminal acetylenes.[8] $Hg(OAc)_2$ was also utilized in the intramolecular solvomercuration of *ortho*-substituted aryl acetylenes to yield indoles.[9] Although perhaps these reactions could not be considered very practical due to the amount and toxicity of the catalysts employed, they revealed the possibility of activation of carbon−carbon triple bonds against nucleophilic attack by amines. From this point, catalytic hydroamination of alkynes has been performed in a variety of ways, using different types of catalysts or initiators and under different reaction conditions.[10] On the other hand, there is still no general and simple method to apply this transformation (particularly at an industrial scale) to all kinds of alkynes and amines.

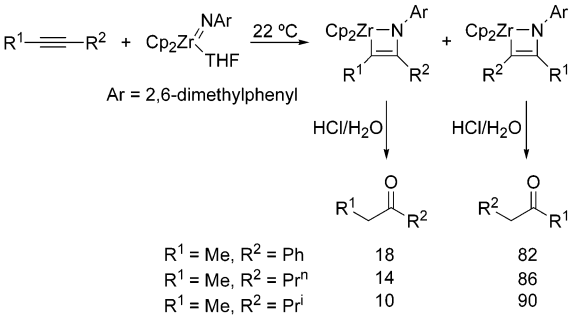
2.1. Early-Transition-Metal Catalysts

Catalysis based on titanium and zirconium complexes has significant advantages compared to that based on some toxic (Hg, Tl) or more expensive metals (Ru, Rh, Pd, U, Th). There are many titanium complexes that can be used as precursors for the active titanium catalyst. Some of them are readily available and relatively cheap while others can be generated in situ, the main difference among them

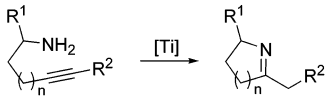
Scheme 2



Scheme 3



Scheme 4



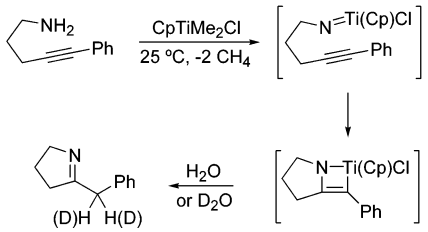
R^1 = H; R^2 = Ph, Bu^n; n = 0
R^1 = Me; R^2 = Ph; n = 0
R^1 = H; R^2 = Ph, Bu^n; n = 1

being the presence or absence of a cyclopentadienyl group (Cp).[11] Nevertheless, it seems to be quite clear that the real catalyst must contain an imido−titanium fragment.

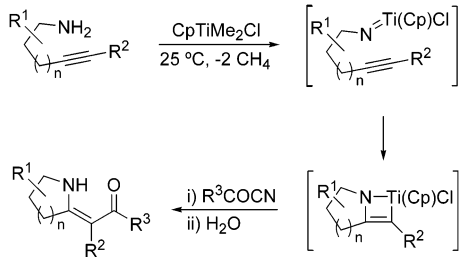
Teuben et al. observed that monomeric titanium complexes of the type $CpTi(NHR)Cl_2$ underwent self-condensation to provide the corresponding imido dimers at room temperature.[12] However, Bergman et al. were the first group to describe several thermally stable monomeric imidozirconocene complexes of the type $Cp_2Zr{=}NR$ and their reactions, in particular with alkynes to form azametallacyclobutenes.[13] Thus, this group utilized bisamides of the type $Cp_2Zr(NHR)_2$, as catalyst precursors, in the addition of 2,6-dimethylaniline to diphenylacetylene (Scheme 2).[14] Besides bisamides $Cp_2Zr(NHAr)_2$, alkyl amides $Cp_2Zr(NHAr)(R)$ were also used, both providing the imido complex $Cp_2Zr{=}NAr$. However, the catalytic hydroamination proceeded slowly and was limited to disubstituted alkynes, also with strong dependence on the reaction conditions. In the stoichiometric reaction, addition of various alkynes to $Cp_2Zr{=}NAr$ at 22 °C occurred regioselectively to furnish the corresponding metallacycles with the larger alkyne substituent located α to the metal center (Scheme 3). Hydrolysis of the metallacycles gave the expected carbonyl compounds through the intermediate enamines and their tautomeric imines.[15]

Livinghouse et al. utilized $CpTiMe_2Cl$ and $CpTiCl_3$ as catalyst precursors for a variety of intramolecular hydroaminations leading to the construction of dihydropyrrole and tetrahydropyridine rings[16] and functionalized tetrahydropyrrole rings (Scheme 4). All compounds were synthesized under mild reaction conditions and in high yields, the proposed mechanism involving the formation of an imido complex,

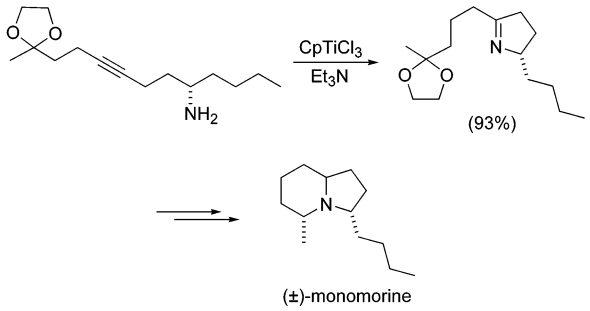
Scheme 5



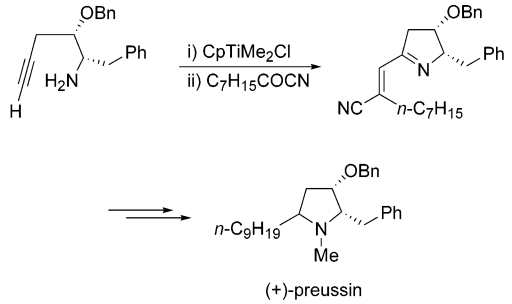
Scheme 6



Scheme 7



Scheme 8

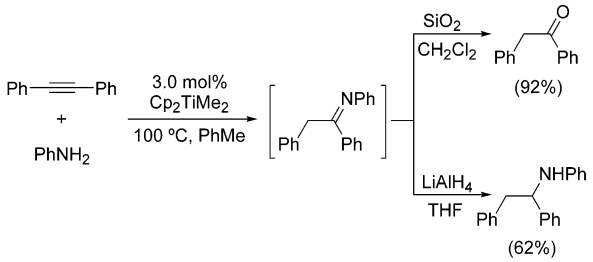


followed by a [2 + 2] cycloaddition, and protonolysis or deuteriolysis (Scheme 5). *C*-Acylation with acyl cyanides of the azatitanacyclobutene as a "living intermediate" provided a range of functionalized tetrahydropyrroles in good to excellent yields (Scheme 6).[17]

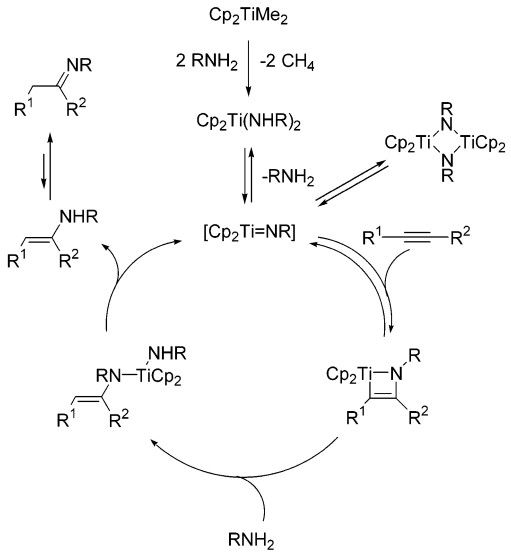
This catalytic imidotitanium−alkyne [2 + 2] cycloaddition methodology was successfully applied to the total syntheses of the indolizidine alkaloid (±)-monomorine (Scheme 7)[18] and the antifungal agent (+)-preussin (Scheme 8).[19]

The catalytic intermolecular hydroamination of alkynes is more difficult to accomplish than the intramolecular version, thus requiring higher temperature.[10i] Doye et al.[20] suggested for this transformation the use of the relatively inexpensive and readily available catalyst Cp_2TiMe_2,[21] which in the presence of an arbitrary amine and by loss of methane would give the catalytically active titanium−bisamide or

Scheme 9



Scheme 10

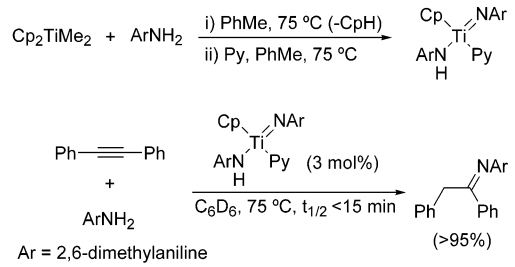


titanium−imido complexes. The enamine forms tautomerized to imines, which due to their potential low stability were subjected to in situ hydrolysis or reduction, furnishing the corresponding carbonyl compounds and amines, respectively (Scheme 9).[20] The yields obtained after hydrolysis were strongly dependent on the nature of the R^1 and R^2 groups in $R^1C{\equiv}CR^2$. For instance, very high yields were observed for $R^1 = R^2 = Ph$ (92%) or $R^1 = Ph$, $R^2 = Me$ (99%), whereas they were very low for $R^1 = R^2 = Et$ (30%) or $R^1 = Ph$, $R^2 = Pr^n$ (35%). On the other hand, no products were observed for terminal alkynes.

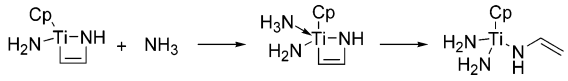
The proposed catalytic cycle includes a reversible [2 + 2] cycloaddition of the alkyne to the imido−titanium complex and cleavage of the Ti−C(sp^2) bond by RNH_2 (protonolysis) in the azatitanacyclobutene, with formation of a bisamide Ti complex, which is thermally transformed into the corresponding enamine and the catalytic species (Scheme 10). The sterically hindered amines were shown to react faster than the less sterically demanding ones, the bulkiness of the substituents seemingly preventing the formation of the nonreactive bisamido and imido−dimer complexes, both in equilibrium with the catalytically active species.[22]

Bergman et al. described the reaction of Cp_2TiMe_2 with an aromatic imine and in the presence of added pyridine, giving an imido complex in which one Cp ligand was exchanged by an amido ligand (Cp−Ti bond protonolysis under the action of $ArNH_2$). This highly active monocyclopentadienyl catalyst precursor was assumed to be formed in alkyne hydroami-

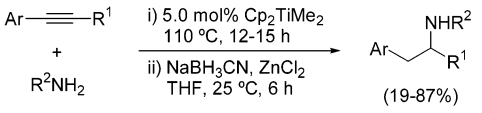
Scheme 11



Scheme 12



Scheme 13



Ar = *m*-$MeOC_6H_4$, *o*-$CF_3C_6H_4$, *p*-$CF_3C_6H_4$, 2-pyridyl
R^1= Pr^n, *c*-C_3H_5, cyclohex-1-enyl
R^2 = *p*-$MeOC_6H_4$, *p*-MeC_6H_4, Bu^t, Bn, Ph_2CH

nation. In fact, this complex rapidly catalyzed the addition of 2,6-dimethylaniline to diphenylacetylene at 75 °C in >95% yield, whereas no reaction was observed with Cp_2TiMe_2 after 12 h under identical conditions (Scheme 11).[23] Certainly, this behavior is not in full agreement with the results presented by Doye et al. (see above).[20]

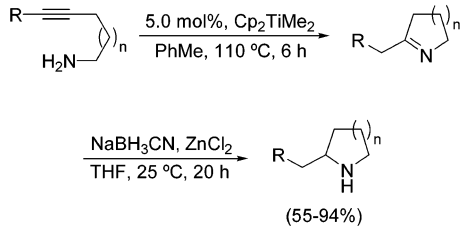
Protonolysis of the titanacycle by the action of the amine is probably the most difficult step to understand in this catalytic cycle. Bergman et al. carried out high-level density functional model calculations on the intermediates involved in this step.[24] The results obtained in the hydroamination of acetylene with ammonia showed that additional coordination of the amine distorted the titanaazacyclobutene with formation of a mesomeric structure, containing a deprotonated dianionic η^3-1-azaallyl ligand that facilitates the proton transfer (Scheme 12).

Doye et al. also reported the one-pot synthesis of 2-arylethylamines starting from alkyl(aryl)alkynes by regioselective hydroamination at the 2-position, the resulting α-arylketimine being in situ reduced to the expected secondary amines with the system $NaBH_4$–$ZnCl_2$·Et_2O (Scheme 13).[25] This methodology seems to work only for aromatic, benzylic, and bulky aliphatic amines.

The same protocol was extended to the intramolecular version of this reaction to afford, after reduction, cyclic amines (Scheme 14).[26] In this case the presence of sterically hindered amines is not required. Nevertheless, the authors noted that this catalytic system does not offer any advantages for intramolecular hydroaminations because the reaction conditions are relatively harsh when compared to most of the other catalytic procedures.[27]

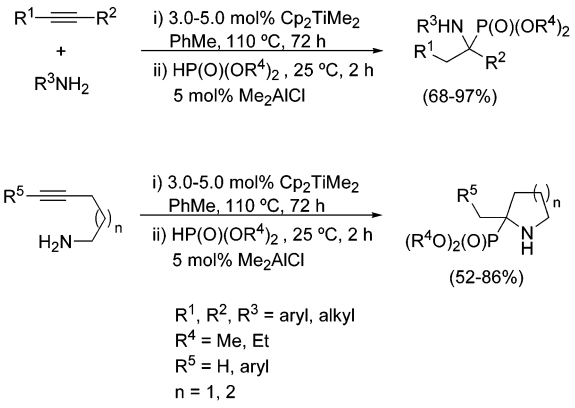
The ketimines generated in these processes can be trapped not only under the action of water or reducing agents, but also with dialkyl phosphites. Thus, Doye et al. described a new one-pot procedure for the

Scheme 14



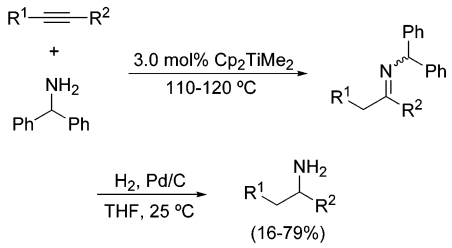
R = H, Hex^n, Ph, *p*-$MeOC_6H_4$, *o*-BrC_6H_4, *o*-$CF_3C_6H_4$, 3,5-$(CF_3)_2C_6H_3$, 2-chloro-5-(trifluoromethyl)phenyl
n = 1,2

Scheme 15



R^1, R^2, R^3 = aryl, alkyl
R^4 = Me, Et
R^5 = H, aryl
n = 1, 2

Scheme 16



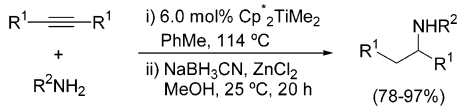
R^1 = Ph, Et, Pr^n
R^2 = Ph, Et, Pr^n, Me, H

synthesis of α,α-disubstituted α-aminophosphonates (an important class of biologically active compounds) consisting of (a) Cp_2TiMe_2-catalyzed hydroamination of an alkyne and (b) nucleophilic addition of a dialkyl phosphite to the resulting imine catalyzed by Me_2AlCl (Scheme 15).[28] The same protocol was applied to the intramolecular reaction.

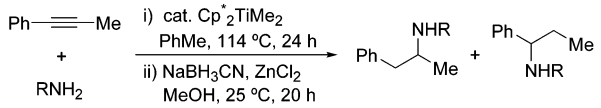
To solve the problem of synthesizing primary amines through hydroamination (the direct use of ammonia is not successful), Doye et al. utilized benzhydrylamine as a convenient ammonia equivalent. The resulting imines were subjected to hydrogenolysis with Pd/C as catalyst to yield the corresponding primary amines. As expected for this catalyst, terminal alkynes gave poor results due to decomposition and byproduct formation (Scheme 16).[29]

The authors suggested the use of the bulkier catalyst $Cp^*_2TiMe_2$ to overcome the unfavorable equilibria between the titanium–imido complexes, imido complex dimers, and bisamides involved in the catalytic cycle and which are believed to be the responsible of the decreased reactivity in the addition of less sterically hindered *n*-alkyl- and benzylamines

Scheme 17



Scheme 18



R	Yield (%)	
p-MeOC$_6$H$_4$CH$_2$	46	36
Hex^n	52	41
Bn	70	24
p-MeC$_6$H$_4$	92	3

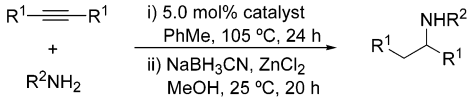
to internal alkynes. All internal alkynes tested gave good results, the yields of amines after reduction with $NaBH_4-ZnCl_2$ being very high (Scheme 17).[30] Unfortunately, when the hydroamination−reduction sequence was applied to unsymmetrically substituted alkynes, mixtures of regioisomers were obtained (except for *p*-MeC$_6$H$_4$NH$_2$), albeit with very high yields (Scheme 18). Control experiments indicated that the low regioselectivity observed with the less sterically demanding *n*-alkyl- and benzylamines could be attributed to the properties of the amines and not to those of the Cp*-ligands. On the other hand, the catalyst was not efficient for the hydroamination of terminal alkynes, byproducts probably derived from oligo- or polymerization being obtained.

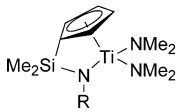
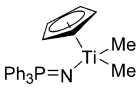
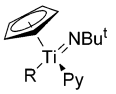
Doye et al. recently studied a wide variety of titanium catalysts for the intermolecular hydroamination of alkynes.[31] The catalytic activities of the titanium compounds were compared in two representative hydroamination−reduction sequences: reaction 1, where R^1 = Ph, R^2 = Bu^t, and reaction 2, where R^1 = Et, R^2 = *p*-Tol (Scheme 19). Most of the catalysts studied gave excellent results for reaction 1 but modest or poor results for reaction 2. In contrast, Cl(Py)CpTi=NBu^t and Ti(NMe$_2$)$_4$ exhibited opposite behavior, the best yields being achieved for reaction 2. Among the dimethyltitanocene complexes, (Ind)$_2$TiMe$_2$ and Cp$_2$TiMe$_2$ can be considered the most general ones.

It is worth noting that microwave-assisted intermolecular hydroaminations catalyzed by Cp$_2$TiMe$_2$ proceeded about 10 times faster in comparison with those conventionally performed in an oil bath at 105 °C, TOF > 10 being achieved by using this technique.[32] Moreover, under these conditions, even terminal alkynes were hydroaminated in reasonable yields, the regioselectivity observed being different for alkylalkynes (mainly leading to the Markovnikov product) and arylalkynes (mainly leading to the anti-Markovnikov product) (Scheme 20).

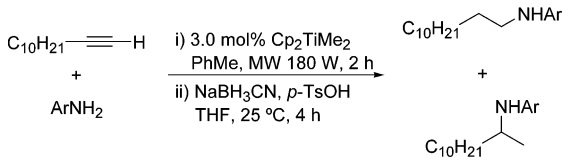
In a recent publication, Beller et al. described the use of two titanocene alkyne complexes of the type Cp$_2$Ti(η^2-Me$_3$SiC≡CR) (R = SiMe$_3$, Ph) (Rosenthal's catalysts)[33] for the hydroamination of internal and

Scheme 19



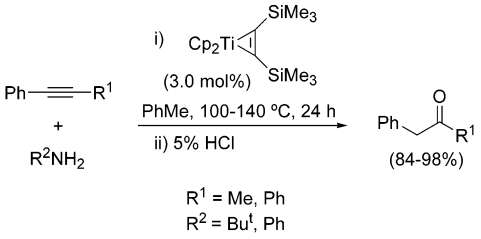
catalyst	R^1= Ph, R^2 = Bu^t Reaction (1)	R^1 = Et, R^2 = *p*-Tol Reaction (2)
R$_2$TiMe$_2$ R = C$_5$H$_4$R' (R' = Me, Et, Pr^i, Bu^t), Cp, Cp*, Ind	81-63%	4-59%
 R = Bu^t	55%	17%
R = Ph	62%	15%
	84%	15%
 R = Cl	46%	93%
R = Cp	98%	43%
Ti(NMe$_2$)$_4$	0%	92%

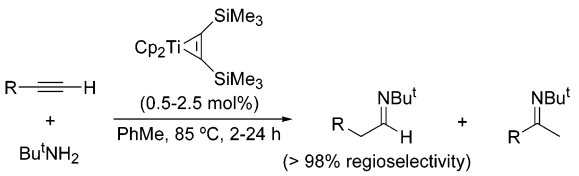
Scheme 20



Ar	linear/branched	Yield(%)
Ph	1 : 7	49
p-Tol	2 : 5	80

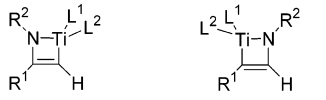
Scheme 21



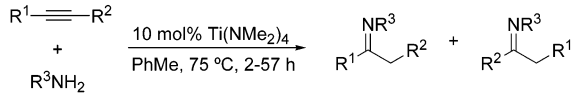


terminal alkynes. Both catalysts gave high yield of products with aromatic and aliphatic amines.[34] However, the catalyst with R = SiMe$_3$ was slightly more active than that with R = Ph (Scheme 21). The most important feature of these catalysts is the fact that they led, very selectively, to the anti-Markovnikov product (63:1 to 100:0) with a variety of aliphatic

Chart 1



Scheme 22



R^1	R^2	R^3	Yield(%)
Et	Et	Ph	87
Ph	Ph	Ph	92
Bu^n	H	Ph	90 (3:1)[a]
Ph	H	Ph	37 (>100:1)[a]
Et	Et	Bu^t	0
Ph	Ph	Bu^t	0
Bu^n	H	Bu^t	0
Ph	H	Bu^t	16 (>100:1)[a]

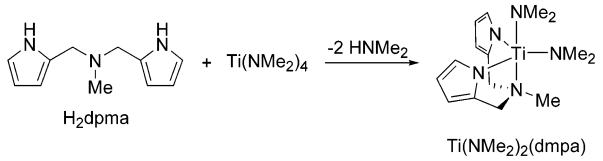
[a] Markovnikov/anti-Markovnikov ratio

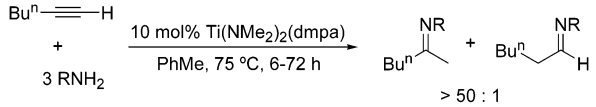
terminal alkynes (including diynes) and Bu^tNH_2. The yield was also very high with less bulky aliphatic amines, the anti-Markovnikov products being obtained preferentially also, though with a decrease in selectivity (2:1 to 4:1). The only exception to this behavior was the reaction of aniline with 1-hexyne, where the Markovnikov product was the major regioisomer (1:3).

It is known that complexes such as Cp_2TiMe_2 and $Ti(NMe_2)_4$ (see below) lead preferentially to the (or exclusive formation for bulky amines) Markovnikov regioisomers in the hydroamination of terminal alkynes. The fact that when Beller used a bulkier catalyst the major product was the anti-Markovnikov one must mean that Cp_2TiMe_2 and $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$ give different intermediates by reacting with amines (Chart 1). Otherwise, the same $Cp_2Ti{=}NR$ intermediate should be involved, and therefore the same result should be obtained with both catalysts.

As already mentioned, alkyne hydroamination catalysis by early transition metals is not only limited to metallocene- or Cp-based systems. Even the simple complex $Ti(NMe_2)_4$ was reported by Odom et al. to find application as a precatalyst in the hydroamination of alkynes with primary amines.[35] Two electronically different amines ($PhNH_2$ and Bu^tNH_2) and four different alkynes were utilized in this study, demonstrating that the Markovnikov products were favored or exclusively formed in the case of starting from terminal alkynes (Scheme 22). However, phenylacetylene led to side reactions and only arylamines seem to give good results. In fact, under these reaction conditions 1-hexyne was subjected to hydroamination with a variety of arylamines, giving rise to the expected imines with moderate to excellent yields and regioselectivities, the formation of the Markovnikov products being again favored. Arylamines bearing strong electron-withdrawing groups, such as pentafluoroaniline, required longer reaction times (96 h), albeit both the yield (75%) and regioselectivity were high (37:1). On the other hand, benzyl and benzhydrylamines gave poor yields (17%).

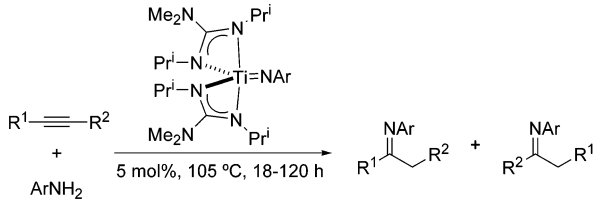
Scheme 23





R = *p*-Tol, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, 3,5-$Cl_2C_6H_3$, C_6F_5, Bn

Scheme 24



Ar = 2,6-dimethylaniline

R^1	R^2	Yield(%)
Me	Me	18
Ph	Ph	55
Bu^n	H	88 (73:27)[a]
Ph	H	94 (14:86)[a]

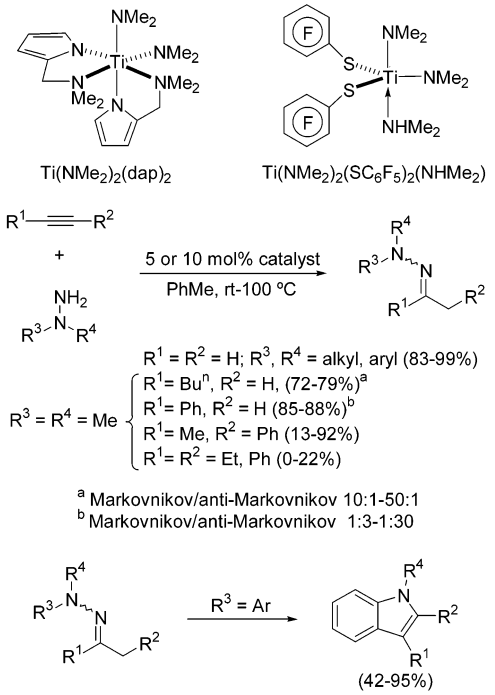
[a] Markovnikov/anti-Markovnikov ratio

Taking into account the dramatic influence of the ligand on the reaction regioselectivity, the same authors tested the new titanium−pyrrolyl complex $Ti(NMe_2)_2$(dpma) generated from $Ti(NMe_2)_4$ and di(pyrrolyl-α-methyl)methylamine (H_2dpma).[36] The new ligand brings new properties to this precatalyst that are different from $Ti(NMe_2)_4$, due to the fact that the ligand remains coordinated to titanium during the reaction. In general, this catalyst, having a bulky ancillary ligand, was more efficient and selective than $Ti(NMe_2)_4$ in the hydroamination with aliphatic and aromatic amines, the selectivity toward the Markovnikov product in the reaction with 1-hexyne also being high (Scheme 23). The reaction with phenylacetylene suffered from oligomerization−polymerization of the alkyne. Although the yields for internal alkynes at 75 °C were modest, in general, they could be improved at 130 °C.

Another attempt to develop an effective and selective titanium-based catalyst was made by Richeson et al.[37] This group prepared an imido complex with two chelating bidentate guanidinate anion moieties. With this catalyst, terminal alkynes reacted more rapidly than internal alkynes in the hydroamination with 2,6-dimethylaniline, though the regioselectivity was low (Scheme 24). However, in contrast with Cp_2TiMe_2, this catalyst was also efficient with less bulky arylamines (e.g., aniline) and aliphatic amines (e.g., cyclohexylamine).

It is known that catalysts such as $Ti(NMe_2)_4$ and $Ti(NMe_2)_2$(dpma), which efficiently catalyze the hydroamination of alkynes with primary amines, are

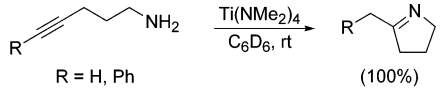
Scheme 25



inefficient for hydrazines. However, Odom et al. developed two new titanium complexes, $Ti(NMe_2)_2(dap)_2$ and $Ti(NMe_2)_2(SC_6F_5)_2(NHMe_2)$, that catalyzed the hydroamination of terminal and some internal alkynes by 1,1-disubstituted hydrazines (but not for hydrazine itself) at 75−100 °C.[38] With 1,1-dimethylhydrazine, hydroamination of internal alkynes was, in general, less efficient, whereas the regioselectivity was dependent on the catalyst used, both favoring Markovnikov addition to 1-hexyne and anti-Markovnikov addition to phenylacetylene, according to the electronic effect of the substituents (Scheme 25). A variety of aryl hydrazines were also tested, the hydroamination of RC≡CH (R = Bu^n, Ph) and $R^1C{\equiv}CR^2$ ($R^1 = R^2 = Ph$; $R^1 = Ph$, $R^2 = Me$) furnishing the corresponding indoles in moderate to high yield, as a modification of the Fisher indole synthesis. The reaction with acetylene was surprisingly easy, proceeding very fast at room temperature, 1 atm, in less than 2 h with $Ti(NMe_2)_2(SC_6F_5)_2(NHMe_2)$, and regardless of the substituents of the 1,1-disubstituted hydrazine, all the corresponding hydrazones were obtained in >80% isolated yield.

Also recently, Bergman et al. reported a comparative study on the catalytic activity of Cp_2TiMe_2 and $Ti(NMe_2)_4$ in the intramolecular hydroamination of aminoalkynes.[39] With the catalyst precursor Cp_2TiMe_2, the terminal alkyne did not react after 12 h at 75 °C; a temperature of 135 °C was necessary to achieve some conversion. Concerning the internal alkyne, conversion was easier and selective at 75 °C, whereas no catalytic activity was observed at room temperature. On the other hand, tetrakisamide precatalyst $Ti(NMe_2)_4$ showed much better effectiveness, the products derived from the terminal and internal alkynes being obtained quantitatively at room temperature in 41 h and 30 min, respectively (Scheme 26).

Scheme 26



During the preparation of this review Bytschkov and Doye published a microreview on the group-IV metal complexes as hydroamination catalysts.[40]

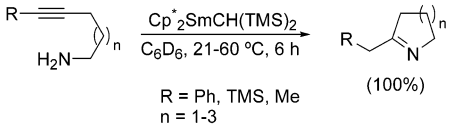
2.2. Lanthanide and Actinide Catalysts

Organolanthanide and organoactinide complexes[41] exhibit unique reactivity for the activation of unsaturated organic compounds as a result of the high electrophilicity of the f-element centers, relatively large ionic radii, absence of conventional oxidative−addition/reductive−elimination steps, and high kinetic lability.[42] Practically parallel to the discovery of the titanium-catalyzed intramolecular hydroamination of alkenes and alkynes, Marks et al. described the catalytic hydroamination−cyclization of aminoalkenes but catalyzed by bis(cyclopentadienyl) derivatives of Ln(III).[43] Organolanthanide and organoactinides have also been used as catalyst precursors for the hydroamination of alkynes, mainly as metallocene complexes.[44] Thus, $Cp^*_2SmCH(SiMe_3)_2$, under rigorously anaerobic reaction conditions, was shown to catalyze the hydroamination−cyclization of a series of aminoalkynes in a regiospecifically manner, with full conversion and good TOFs (up to >7600), giving rise to cyclopenta-, cyclohexa-, and cycloheptaimines (Scheme 27).[45] A deceleration in the rate was observed when the more open complex $Me_2Si(\eta^5\text{-}Me_4C_5)_2SmCH(SiMe_3)_2$ was used as the catalyst. The proposed catalytic cycle is different from the Ti (Zr)- or Pd (Rh)-catalyzed reaction, no conventional oxidative addition−reductive elimination processes being involved. Thus, it was suggested that the amino group in the starting alkyne was able to cleave the Ln−C bond in $Cp^*_2LnCH(SiMe_3)_2$ to give the corresponding amide, followed by carbon−carbon triple-bond insertion into the Ln−N bond and rapid protonolysis of the resulting Ln−C bond (Scheme 28). The above-mentioned insertion step was estimated to be about 35 kcal/mol more exothermic than for olefins.[46]

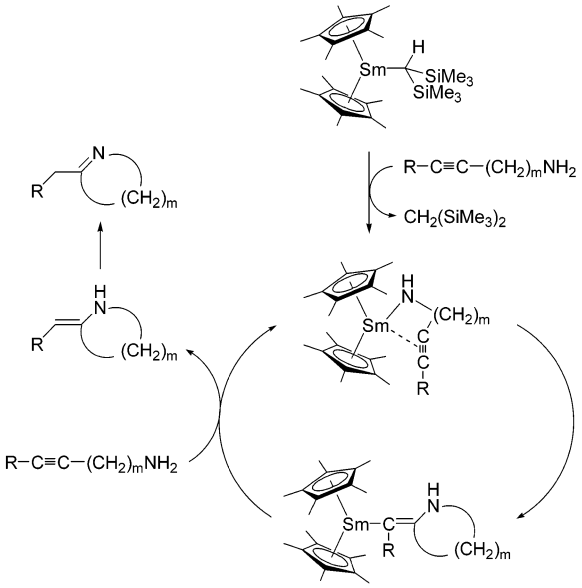
In a deeper study, this group extended the methodology to intramolecular hydroamination of a wide range of substrates, including not only primary and secondary amines but also internal and terminal alkynes.[47] In this case, the metal and ancillary ligation effects were compared for different catalysts of the type $Cp^*_2LnCH(SiMe_3)_2$ (Ln = La, Nd, Sm, Lu) and $Me_2Si(\eta^5\text{-}Me_4C_5)_2LnCH(TMS)_2$ (Ln = Nd, Sm). Thus, a deceleration in the rate was observed when larger ionic radius Ln^{3+} catalysts or more open $Me_2Si(\eta^5\text{-}Me_4C_5)_2Ln$ coordination spheres were utilized.

The same type of complexes also catalyzed the intermolecular hydroamination of primary aliphatic

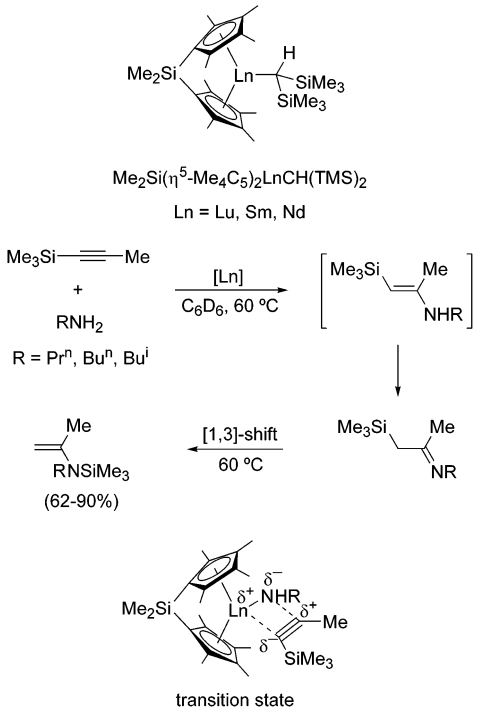
Scheme 27



Scheme 28



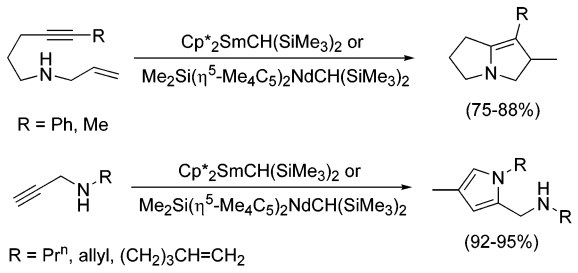
Scheme 29



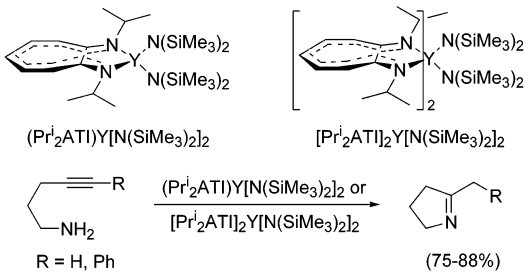
amines and internal alkynes in good to excellent yields at 50−60 °C but with low TOFs.[48] In comparison with the intramolecular hydroamination process, the latter was up to ∼1000 times more rapid, the greatest intermolecular alkyne hydroamination rates being achieved for silyl-substituted acetylenes. Starting from these silyl-substituted alkynes, the initial imine insertion products underwent a 1,3-sigmatropic silyl shift, the regiochemistry of the products being in concordance with the stabilizing tendency by silicon atoms of α-carbanionic and β-carbocationic centers (Scheme 29).

This approach was used for intra- and intermolecular tandem C−N and C−C bond-forming reactions of aminoalkynes, aminoalkeneynes, and aminodialkynes, thus giving direct access to pyrrolizidine, pyrrole, and pyrazine skeletons (Scheme 30).[49] The rate of bicyclization decreased by the presence of sterically encumbered substituents for the same alkyne−alkene framework, whereas an acceleration was observed when increasing the ionic radii of the lanthanide (in marked contrast to the analogous hydroamination−cyclization of aminoalkynes, see above).

Scheme 30



Scheme 31

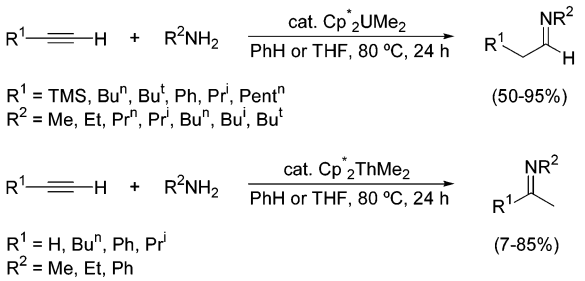


Not only lanthanocenes but some other Cp-free complexes can also catalyze the intramolecular hydroamination of alkynes. Thus, Roesky et al. synthesized mono- and bis-[*N*-isopropyl-2-(isopropylamino)-troponiminato]yttrium amides $(Pr^i_2ATI)Y[N(SiMe_3)_2]_2$ and $(Pr^i_2ATI)_2Y[N(SiMe_3)_2]_2$ (ATI = aminotroponiminate), which proved to be active, the reaction proceeding regiospecifically to completion in benzene (Scheme 31).[50] However, the activity observed for these complexes was significantly lower in comparison with that showed by $Cp_2{}^*YCH(SiMe_3)_2$. Under the same reaction conditions, the chloro compounds $(Pr^i_2ATI)YCl_2(THF)_2$ and $(Pr^i_2ATI)_2YCl$ exhibited even lower catalytic activities than those observed for the above-mentioned complexes.

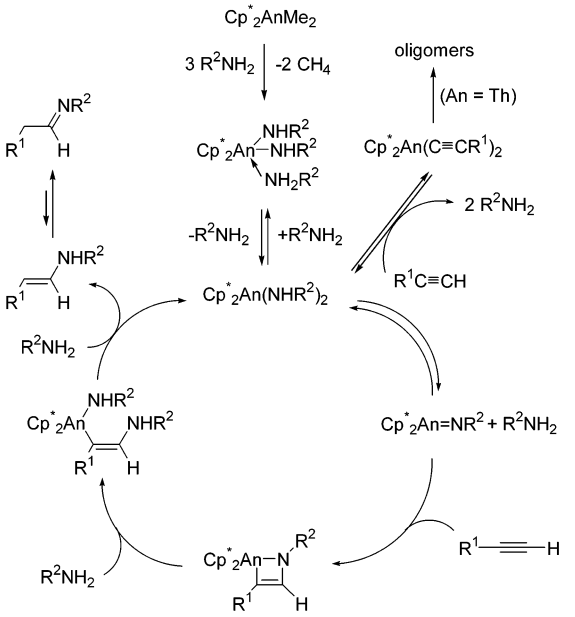
The same reaction depicted in Scheme 31 was utilized as a model transformation to test the catalytic activity of homoleptic bis(trimethylsilyl)amides of lanthanides of the general type $Ln[N(SiMe_3)_2]_3$ (Ln = Y, La).[51] These readily available complexes catalyzed the hydroamination−cyclization of aminoalkynes at 60 °C in high yield (71−100%). In general, the complex with Ln = Y gave better results, albeit the catalytic activity of both complexes at 60 °C was much lower than that of $Cp^*_2YCH(SiMe_3)_2$ at 21 °C. This behavior was explained in terms of the absence of any ancillary ligands in the homoleptic amines.

Eisen et al. reported the reactivity and selectivity of actinide catalysts of the type $Cp^*_2AnMe_2$ (An = U, Th) in the intermolecular hydroamination of terminal alkynes by aliphatic primary amines.[52] The chemoselectivity and regioselectivity of the reactions were shown to depend strongly on the nature of the

Scheme 32



Scheme 33



catalyst and the bulkiness of the amine, with less dependence on the alkyne nature. Thus, regioselective anti-Markovnikov formation of the corresponding imines was achieved in high yields with $Cp^*_2UMe_2$, the imine derived from $HC{\equiv}CSiMe_3$ undergoing 1,3-shift of the TMS group. However, $Cp^*_2ThMe_2$ showed less chemoselectivity, lower yields being obtained as a result of partial alkyne oligomerization, and surprisingly leading to opposite regioselectivity (Markovnikov, except for $HC{\equiv}CSiMe_3$) (Scheme 32). Although most of the yields with $Cp^*_2ThMe_2$ are within the range 7−33%, this complex allowed the unique alkyne hydroamination with an aromatic amine reported in this work, which in addition also occurred with high yield (85%).

The mechanistic study of the above reactions allowed the catalytic cycle depicted in Scheme 33 to be proposed. The first step involves N−H σ-bond activation to give an organoactinide bis(amido)amine complex, in rapid equilibrium with the corresponding bis(amido) complex. This bis(amido) complex may follow a σ-bond metathesis with the terminal alkyne, yielding $Cp^*_2An(C{\equiv}CR^1)_2$, which can induce the production of oligomerization products (only for Th complexes). However, the bis(amido) complex can also loose an amine molecule, leading to an imido−actinide complex $Cp^*_2An{=}NR^2$ (the rate-determining step), which undergoes double-bond metathesis ([2 + 2] cycloaddition) with the alkyne (anti-Markovnikov) and subsequent protonolytic ring opening by the amine, giving an enamide amido organoactinide complex. The latter complex reacts with the amine, yielding the starting bis(amido) complex and the enamine, which rapidly isomerizes to the corresponding imine.

The mechanism suggested is practically the same as that proposed for the intermolecular hydroamination of terminal alkynes catalyzed by titanocene- and zirconocene-based complexes (see Scheme 10)[22] but in which the Markovnikov adduct was preferentially formed, above all in the reaction with arylamines (see Scheme 20).[32] On the other hand, Beller's titanocene catalysts led exclusively to anti-Markovnikov regioisomers with primary alkylamines (see Scheme 21).[34] Perhaps the main difference between the early-transition-metal and lanthanide and actinide catalytic cycles is the fact that for the former, bond protonolyses follow the order Ti−C(sp^2) before Ti−N whereas for the latter the order appears reversed, An−N before An−Csp^2; the same type of products are obtained in both cases.

It is also worthwhile to establish a comparison between this actinide catalysis work and that reported by Marks et al.[48] in the intermolecular hydroamination of alkynes catalyzed by lanthanide Cp complexes. Here, only terminal alkynes undergo hydroamination whereas internal alkynes do not, the silyl substituent effects being minor. The metal-dependent effects on regiochemistry are only observed for the actinide but not for the lanthanide complexes. Finally, the kinetics is zero-order in amine, first order in Ln, and first order in alkyne concentrations for the lanthanide complexes catalysis, whereas it is zero-order in alkyne, first order in An, and inverse order in amine concentrations for the actinide complexes catalysis, thus involving a metal−imido intermediate in the latter case.

2.3. Late-Transition-Metal Catalysts

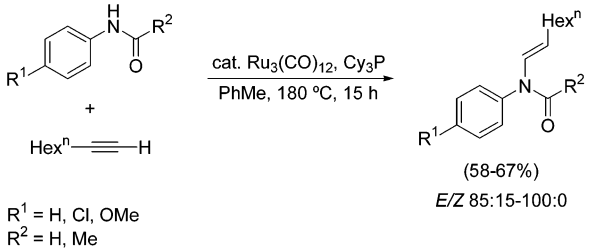
One main advantage of introducing late transition metals in the complexes used as catalysts for the title process, in comparison with early transition metals, lanthanide, and actinide metals, is the fact that the low oxophilicity of the former allows compatibility with many substrates that would be excluded in the catalysts with highly oxophilic metals.

2.3.1. Ruthenium

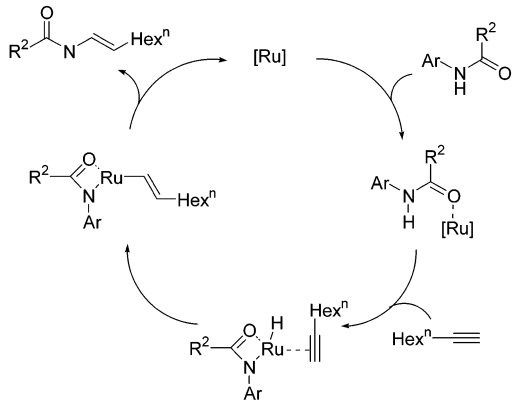
One of the first examples of intermolecular hydroamination of alkynes catalyzed by ruthenium compounds is that reported by Heider et al. In this patent, $RuCl_3$ was used as catalyst in the reaction of acetylene with an amine (e.g., 2-pyrrolidone, imidazole, or succinimide), performed in a reactor heated at 50−250 °C and at 1−30 bar, giving the corresponding *N*-vinyl compound in high yield (e.g., 87% yield for *N*-vinyl-2-pyrrolidone).[53]

Also, in the mid 1990s Watanabe et al. discovered that the $Ru_3(CO)_{12}$−PCy_3 system was an effective catalyst for the addition of *N*-aryl-substituted amides to oct-1-yne.[54] The $Ru_3(CO)_{12}$−PCy_3 and Ru(COD)(COT)−PCy_3 systems also showed high catalytic activities, the corresponding (*E*)-enamides being obtained in all cases with high regio- and stereoselec-

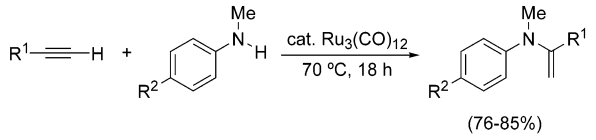
Scheme 34



Scheme 35



Scheme 36

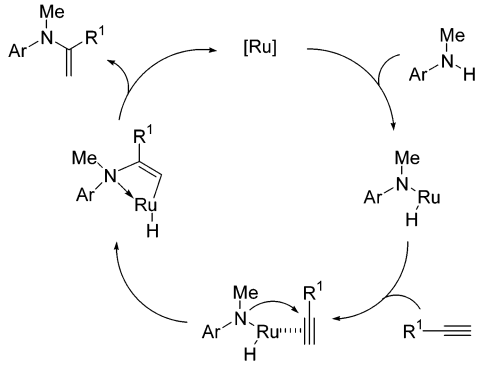


tivity (Scheme 34). The reaction proceeded with anti-Markovnikov regioselectivity and was restricted to *N*-aryl amides, since *N*-alkyl amides led to intractable mixtures. A reaction mechanism was proposed with initial coordination of the *N*-aryl-substituted amide to the active zerovalent ruthenium complex, followed by alkyne coordination, oxidative addition to the N−H bond, and alkyne insertion. Finally, the reductive elimination furnished the enamide, regenerating the active zerovalent ruthenium species (Scheme 35).

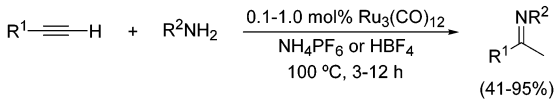
On the other hand, the addition of amines to alkynes catalyzed by ruthenium complexes can be considered a more recent research field. In fact, it was in 1999 when Uchimaru and Wakatsuki et al. reported separately the first examples of ruthenium-complex-catalyzed addition of amines to terminal alkynes.

Uchimaru described the hydroamination of aryl and cycloalkenyl alkynes with secondary *N*-methyl anilines catalyzed by $Ru_3(CO)_{12}$, giving rise to the corresponding *N*-methyl-*N*-(α-styryl)anilines as a result of the regioselective Markovnikov addition (Scheme 36).[55] $[Ru(CO)_3Cl_2]_2$ also promoted this reaction but was less effective, whereas other transition-metal complexes such as $[Ru(p\text{-cymene})Cl_2]_2$, $Ru(PPh_3)_3Cl_2$, $[Ru(COD)Cl_2]_n$, $[CpRu(CO)_2]_2$, $Fe(CO)_5$, $Co_2(CO)_8$, $Co_4(CO)_{12}$, $Pd(PPh_3)_2Cl_2$, and Cp_2ZrMe_2 were ineffective. A reaction mechanism was proposed involving the oxidative addition of the N−H bond of

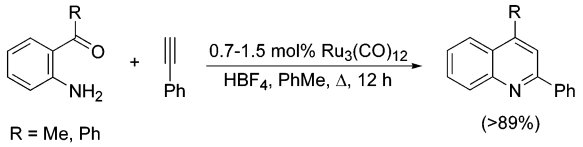
Scheme 37



Scheme 38



Scheme 39

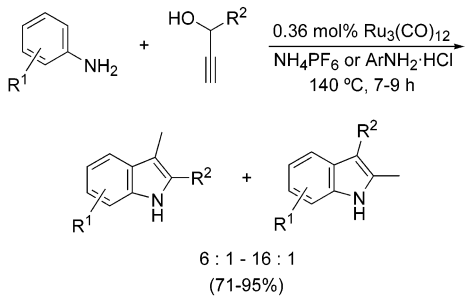


the amine to Ru(0), followed by coordination of the alkyne to the ruthenium center, intramolecular nucleophilic attack of nitrogen on the coordinated carbon−carbon triple bond, and final reductive elimination (Scheme 37).

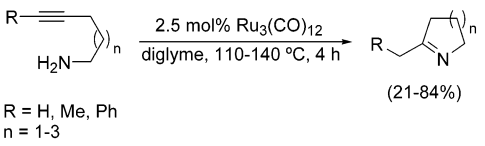
Wakatsuki's group also notably contributed to the addition reactions to alkynes catalyzed by ruthenium complexes.[56] This group observed a great acceleration in the above-described reaction by addition of strong acids such as HPF_6 and HBF_4 or their ammonium salts (Scheme 38).[57] For instance, with 0.1 mol % $[Ru_3(CO)_{12}]$ and 0.3 mol % NH_4PF_6 the reaction of phenylacetylene and aniline was completed in 12 h at 100 °C, giving the corresponding Markovnikov imine in 84% yield, only 2.6% yield being obtained under the same reaction conditions but in the absence of the additive. It is noteworthy that the reaction can be performed in air and that the highest reaction rate was achieved for the solvent-free system. However, aliphatic acetylenes were found to be less reactive than phenylacetylene. This methodology could be successfully extended to a 50-g-scale reaction (92% yield, >99% purity, TON = 300) and to the synthesis of 2,4-disubstituted quinolines starting from *o*-acylanilines (Scheme 39). On the other hand, the enhancement effect of the additives remains unclear, though the authors suggest that protons must play an important role in this process.

The above-described procedure was applied to the regioselective preparation of 2,3-disubstituted indoles from anilines and propargyl alcohols (Scheme 40).[58] The hydroamination key step was performed with catalytic $Ru_3(CO)_{12}$ in the presence of small amounts of additives NH_4PF_6 or $ArNH_2{\cdot}HCl$. Subsequent

Scheme 40



Scheme 41



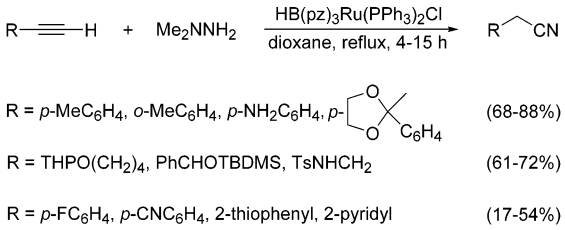
hydrogen migration of the resulting amino alcohol to the corresponding aminoketone and final cyclization furnished the indole moiety in high yields [except for methyl *o*-aminobenzoate (5%)]. $Ru(PPh_3)_2Cl_2$ showed similar activity to $Ru_3(CO)_{12}$ in this one-pot indole formation (140 °C) but low activity for the first amination step (100 °C).

According to Müller's report, and in contrast with the above demonstrated effectiveness of complex $Ru_3(CO)_{12}$ in intermolecular hydroaminations, this complex was not efficient for intramolecular hydroaminations.[59] Thus, intramolecular hydroamination of 6-aminohex-1-yne to 2-methyl-1,2-dehydropiperidine was accomplished in only 21% yield after 20 h at 40 °C in CH_2Cl_2. Nonetheless, a conversion higher than 18% (at 40 °C) might be expected if the reaction was carried out at a higher temperature. No reaction was observed when $Ru(PPh_3)_2Cl_2$ was used as catalyst.

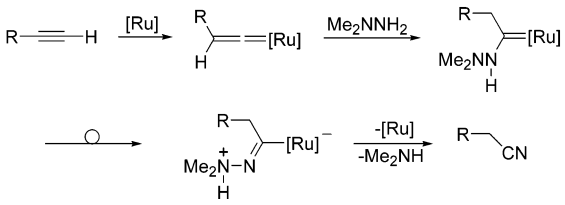
On the other hand, Mitsudo et al. tested a large variety of low-valent ruthenium complexes for the intramolecular hydroamination of alkynes, those complexes bearing a π-acidic ligand showing good to high catalytic activity.[27] In contrast with Müller's results, Mitsudo's work describes $Ru_3(CO)_{12}$ and $Ru(\eta^6\text{-COT})(dmfm)_2$ as the best catalysts, other complexes such as $(\eta^3\text{-}C_3H_5)RuBr(CO)_3$, $[Ru(CO)_3Cl_2]_2$, and $Ru(CO)_3(PPh_3)_2$ also showing good catalytic activity. However, catalytic activities of zero- and divalent ruthenium complexes without a π-acidic ligand, such as $Ru(\eta^4\text{-COD})(\eta^6\text{-COT})$, $Ru(\eta^5\text{-cyclooctadienyl})_2$, $[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$, Cp*Ru(COD)Cl, $Ru(PPh_3)_3Cl_2$, and $Ru(PPh_3)_4H_2$, were moderate to low. When a series of alkynes differing in length ($n = 1-3$) and substitution were subjected to $Ru_3(CO)_{12}$-catalyzed intramolecular hydroamination, the expected five-, six-, and seven-membered nitrogen-containing heterocycles and indoles were obtained in good to high yields (Scheme 41). The cyclization rates and product yields, as a function of ring size, followed the trend $5 > 6 \gg 7$, a reaction mechanism similar to that depicted in Scheme 37 being proposed.

The titanium-catalyzed intermolecular hydroamination of both internal and terminal alkynes with

Scheme 42



Scheme 43



hydrazines to yield the corresponding hydrazones was described above (see Scheme 25 in section 2.1). However, and in a different mechanistic context, Fukumoto et al. reported the reaction of terminal alkynes with hydrazines catalyzed by ruthenium complexes leading to nitriles.[60] Although several ruthenium catalysts were active in this interesting transformation, $HB(pz)_3Ru(PPh_3)_2Cl$ [$HB(pz)_3$ = tris(pyrazolyl)borate] showed the highest catalytic activity. These reactions, performed in refluxing dioxane, were applicable to differently substituted hydrazines, *N*,*N*-dimethylhydrazine being the hydrazine of choice. Thus, the $HB(pz)_3Ru(PPh_3)_2Cl$-catalyzed reaction of *N*,*N*-dimethylhydrazine with a wide variety of terminal alkynes led to the corresponding nitriles in moderate to good yields (Scheme 42). In general, the highest yields were obtained for phenylacetylenes with electron-donating groups at the *para*-position.

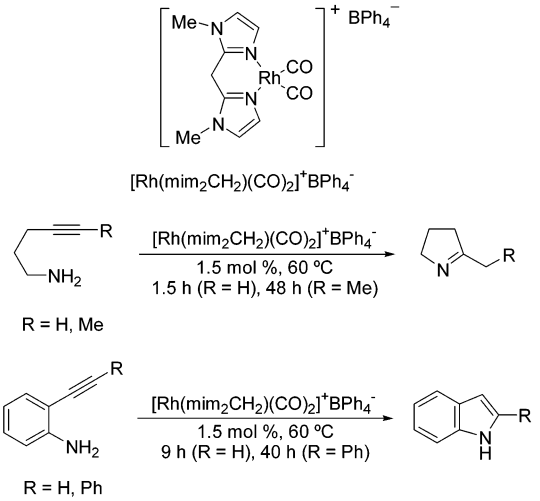
The reaction mechanism was proposed to involve a ruthenium−vinylidene complex,[61] which suffers nucleophilic attack by the hydrazine (giving an α-hydrazinocarbene complex), followed by proton migration (leading to a zwitterionic complex), and finally deamination (Scheme 43). The above-described reaction can be considered the first example of catalytic intermolecular attack of a nitrogen nucleophile on a (vinylidene)metal intermediate.

2.3.2. Rhodium

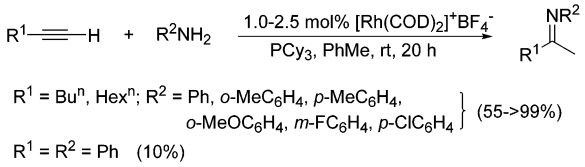
There are very few rhodium catalysts that promote the catalytic addition of amines to alkynes. In fact, even the stoichiometric reaction of $[Rh(CO)_2Cl]_2$ with alkynylamines of the type $ArC{\equiv}C(CH_2)_nNH_2$ ($n = 2$, 3) was shown to be inefficient, the resulting alkynylamine dicarbonyl rhodium(I) complex requiring very long reaction times for cyclization and the 2-substituted pyrroline derivatives being obtained in low yields. Attempts to convert this reaction into a catalytic process were unsuccessful.[62]

On the other hand, Müller et al. found that the catalytic intramolecular hydroamination of 6-aminohex-1-yne with rhodium(I) compound [Rh(COD)(DIPAMP)]BF_4 in toluene after 20 h at 111 °C led to 2-methyl-1,2-dehydropiperidine in 59% yield (80% conversion). However, no catalytic activity was observed for the rhodium(III) compound $[RhI_2(COD)]$-

Scheme 44



Scheme 45

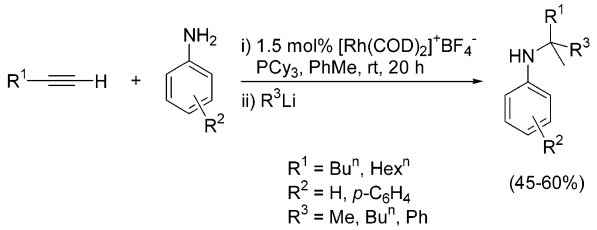


Cl.[59,63] Higher catalytic activity in this reaction was observed when a rhodium(I)-exchanged zeolite (BEA) was utilized as heterogeneous catalyst.[64]

The cationic Rh(I) dicarbonyl complex $[Rh(mim_2CH_2)(CO)_2]^+BPh_4^-$, containing a bidentate bisimidazolylmethane ligand (mim = *N*-methylimidazol-2-yl), was synthesized by Messerle et al.[65] and proved to be an effective catalyst for the intramolecular hydroamination of aliphatic and aromatic alkynes (Scheme 44).[66] Aliphatic internal alkynes reacted slower than terminal ones but regioselectively, whereas alkynylanilines gave the expected indoles with complete conversion. Although the mechanism seems to be under investigation, the authors have not detected the formation of metal hydrides, metal-coordinated enamines, or free CO. Other cationic Rh(I) catalysts tested revealed a strong dependence of the activity on the ligand donor and nature of the counterion.

The first rhodium-catalyzed intermolecular hydroamination of alkynes was presented by Beller et al.[67] After testing different rhodium complexes and reaction conditions, the best results were obtained with the cationic Rh(I) complex $[Rh(COD)_2]^+BF_4^-$ in combination with the phosphine ligand PCy_3, using not strongly coordinating solvents (toluene, THF, dioxane) at room temperature (which minimizes oligomerization). Good yields of the Markovnikov's product were obtained for alkyl acetylenes and anilines, electron-withdrawing substituents on the aniline moiety reacting faster and rapid oligomerization occurring for phenylacetylene (Scheme 45). The reaction of phenylacetylene with morpholine furnished the corresponding anti-Markovnikov product but only in 15% yield. On the other hand and taking advantage of the absence of water as byproduct in this reaction (in contrast with the imine formation method by amination of carbonyl compounds), a one-pot strategy was settled for the synthesis of branched amines by trapping the intermediate imine, resulting from hydroamination, with organolithium reagents (Scheme 46). Although the cationic character of the catalyst seems to be essential to activate the alkyne component and induce the nucleophilic attack of the amine, an amine activation pathway was not ruled out.

Scheme 46

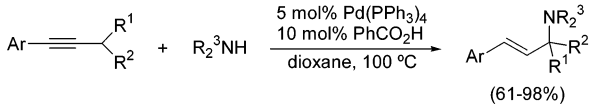


2.3.3. Palladium

Palladium[68] is by far the most utilized metal in the catalytic hydroamination of alkynes, above all in the intramolecular fashion.[10l,m] Thus, η^2-alkyne−organopalladium complexes derived from alkynes and containing an amino group close to the acetylenic moiety can suffer intramolecular nucleophilic attack across the carbon−carbon triple bond to afford the corresponding heterocyclic compounds. This methodology has demonstrated its value in the synthesis of a variety of structurally different heterocycles, in particular in the synthesis of indoles.[69] Nevertheless, we will deal first with the few examples known of intermolecular hydroaminations, the intramolecular processes being treated later on with special emphasis on the synthesis of indoles.

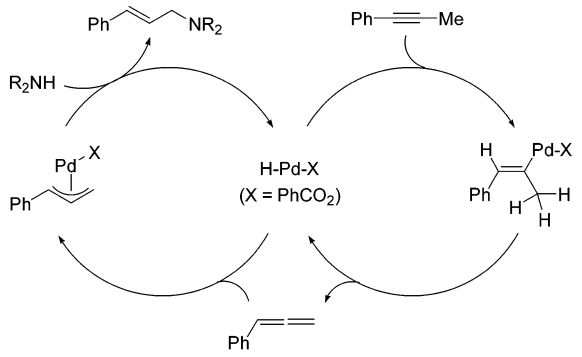
Concerning intermolecular hydroaminations, Yamamoto et al. reported the hydroamination of various aromatic internal alkynes with secondary amines in the presence of 5 mol % $Pd(PPh_3)_4$ and 10 mol % benzoic acid in dioxane at 100 °C, furnishing the corresponding allylic amines with good to excellent yields (Scheme 47).[70] The presence of benzoic acid

Scheme 47

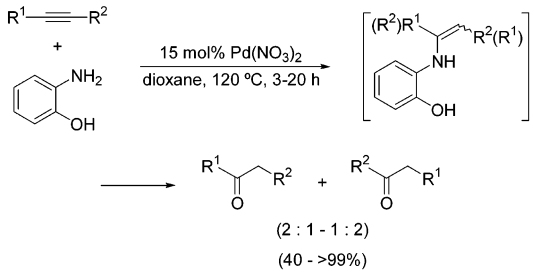


was essential for the reaction to occur, better yields being obtained for substrates bearing electron-donating groups on the aromatic ring. The reaction with primary amines led to the corresponding double-hydroaminated products, whereas no reaction was observed for aliphatic acetylenes, independent of the type of amine. The proposed catalytic cycle includes the hydropalladation of the alkyne [with hydridopalladium species formed from Pd(0) and benzoic acid], formation of an arylallene and the active catalyst H−Pd−X (via β-elimination), hydropalladation of the arylallene to give a π-allylpalladium species, and reaction of the latter with the amine to furnish the product and the active catalyst (Scheme 48). This

Scheme 48



Scheme 49



R^1 = Pent^n, Ph, $C_{10}H_{21}{}^n$, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *p*-$CF_3C_6H_4$
R^2 = H, Me, Bu^n, Pent^n, Ph, $(CH_2)_4X$ (X = OMe, OBn, OAc, OTBDMS, Cl)

methodology was demonstrated to be effective also in the intramolecular hydroamination of alkynes, leading to the formation of allylic pyrrolidines and piperidines.

More recently, the same group presented the intermolecular hydroamination of terminal and internal alkynes with *o*-aminophenol catalyzed by Pd-$(NO_3)_2$, which after hydrolysis led to the corresponding carbonyl compounds in moderate to excellent yields (Scheme 49).[71] The high-yielding hydroamination of internal alkynes furnished a mixture of regioisomers (1:2 to 2:1), whereas lower yields were obtained for terminal alkynes due to competitive cyclotrimerization, albeit very regioselective in favor of the Markovnikov product. Other palladium catalysts tested, such as $Pd_2(dba)_3{\cdot}CHCl_3$, $PdCl_2$, Pd-(acac)$_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$, Na_2PdCl_4, Pd(dppf)Cl_2, and $Pd(MeCN)_2Cl_2$, though also active gave lower yields (47−68%). Unfortunately, this methodology could not be extended to aliphatic amines, aniline, or other substituted anilines, affording the products in <50% yield. The presence of the hydroxy group at the *ortho*-position seemed to be crucial to enhance the rate of hydroamination, since other arylamines such as *m*- and *p*-hydroxyaniline achieved yields of only 48% and 30%, respectively. Although the mechanism of the reaction remains uncertain, participation of either an *o*-hydroxyamidopalladium(II) complex (which would undergo 1,2-insertion of the alkyne moiety) or a H−Pd−(2-aminophenoxide) species [generated from 2-aminophenol and Pd(0)] was suggested, which would undergo tautomerization to an amidopalladium species and subsequent reductive elimination.

Leung et al. accomplished the synthesis of the six-membered heterocycle 1,4-2*H*-1,2,4,6-tetraphenyl-1,4-azaphosphabenzene through a palladium(II)-promoted hydroamination between di(phenylethynyl)-

Scheme 50

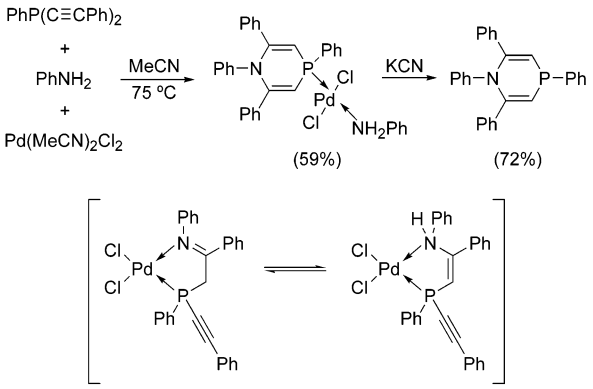
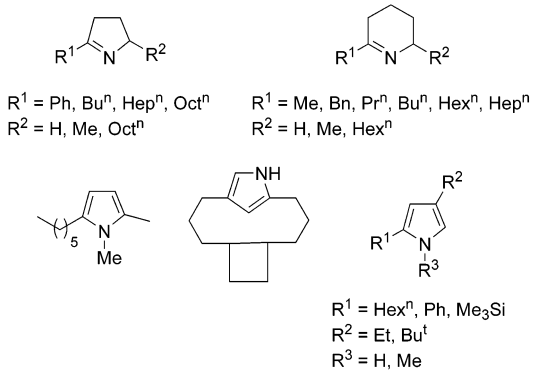


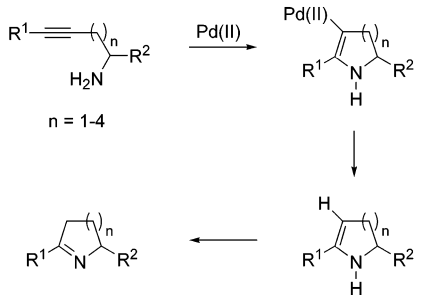
Chart 2. Cyclic Imines and Pyrroles Obtained by $PdCl_2$-Catalyzed Intramolecular Hydroamination of Aminoalkynes and 1-Amino-3-alkyn-2-ols, Respectively



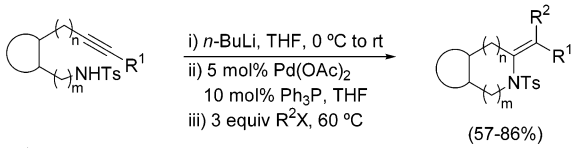
phenylphosphine and aniline.[72] The reaction proceeded smoothly with a stoichiometric amount of Pd-$(MeCN)_2Cl_2$ and an excess of aniline in acetonitrile at 75 °C, giving rise to an aniline−ligand-coordinated complex, which after treatment with potassium cyanide liberated the expected six-membered P−N heterocycle (Scheme 50). From a mechanistic point of view, the experimental data seem to support the stepwise reaction involving iminophosphine and/or enamino phosphine complexes (resulting from the intermolecular hydroamination), which undergo further intramolecular hydroamination. On the other hand, no comment was made concerning the regioselectivity of the reaction.

Concerning the intramolecular hydroamination of alkynes, Utimoto described in a seminal work that the amino group could be added to acetylenic bonds intramolecularly by the catalytic action of $PdCl_2$ in refluxing acetonitrile. Under these reaction conditions, a series of alkynylamines and 1-amino-3-alkyn-2-ols were transformed into the corresponding cyclic imines and differently substituted pyrroles (Chart 2). Although $Pd(OAc)_2$ could be used instead of $PdCl_2$ as catalyst, less effectiveness was observed with Pd-$(PPh_3)_4$.[73] This methodology was extended to other aliphatic aminoalkynes, giving rise to the formation of 1-pyrrolines (from 3-alkynylamines), 2,3,4,5-tetrahydropyridines (from 5-alkynylamines), and mixtures of both five- and six-membered cyclic imines (from 4-alkynylamines). Unfortunately, application to the synthesis of larger cyclic imines was unsuccessful.[74] These reactions were explained in terms of

Scheme 51

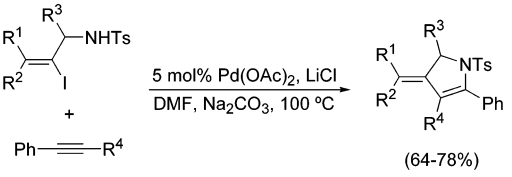


Scheme 52



R^1 = H, Me
R^2 = Ph, heteroaryl, alkenyl
n = 1, 2; m = 0, 1
X = Br, I

Scheme 53



R^1-R^2 = $(CH_2)_5$, R^3 = H, R^4 = Ph
R^1 = R^2 = Me, R^3 = H, R^4 = Ph
R^1 = Me, R^2 = Ph, R^3 = H, R^4 = Ph
R^1-R^3 = $CMe_2CH_2CH_2$, R^2 = H, R^4 = Ph
R^1-R^3 = $CMe_2CH_2CH_2$, R^2 = H, R^4 = CO_2Et

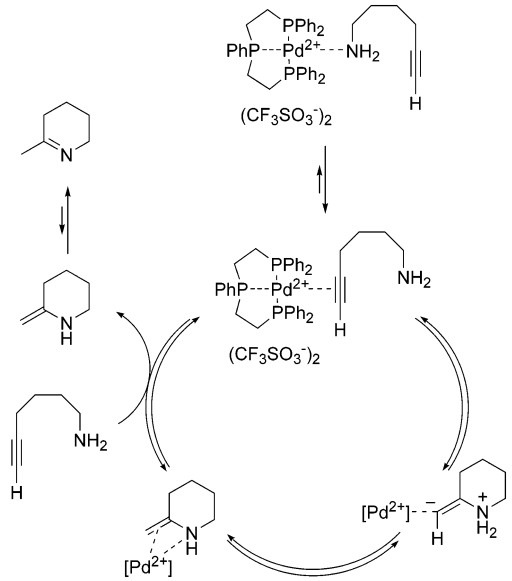
intramolecular aminopalladation (giving intermediary alkenylpalladium compounds) and protonolysis of the C−Pd bond (accelerated by the presence of water), initially leading to cyclic enamines that isomerized to the thermodynamically more stable cyclic imines (Scheme 51).

Luo et al. showed that the intermediate alkenylpalladium species resulting from intramolecular hydroamination could be easily trapped with different organic halides.[75] Thus, tandem intramolecular aminopalladation of acetylenic amines, followed by cross-coupling reaction with organic halides, furnished a wide range of stereodefined monocyclic and bicyclic 2-alkylidene-pyrrolidine and piperidine derivatives (Scheme 52). The reactions were performed by treatment with *n*-BuLi, catalytic amounts of $Pd(OAc)_2$ and Ph_3P in THF, and an excess of the organic halide.

Larock et al. synthesized a series of substituted 2,3-dihydro-1*H*-pyrroles by palladium-catalyzed coupling of vinyl iodides and internal alkynes, followed by intramolecular amination with the sulfonamide functionality (Scheme 53).[76] The reaction with ethyl phenyl propiolate was regioselective, whereas with 4,4-dimethyl-2-pentyne mixtures of stereoisomeric unsaturated aldehydes were obtained.

In Müller's reports about the cyclization of 6-aminohex-1-yne to 2-methyl-1,2-dehydropiperidine catalyzed by transition metals, different palladium(II)

Scheme 54

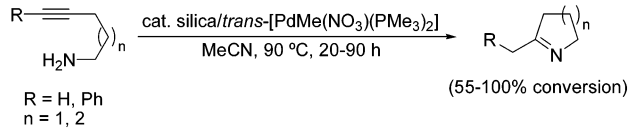


catalysts were moderately effective for this transformation.[59,63] $[Pd(MeCN)_4](BF_4)_2$, $[Pd(dppf)](NO_3)_2$, and $[Pd(Triphos)](BF_4)_2$ led to reaction yields in the range 52−77%, though $[Pd(dppf)](NO_3)_2$ exhibited very low conversion (5%). In contrast, no conversion was obtained with either palladium(0) compounds such as $Pd(PBu^t_3)_2$ and $Pd(dppf)_2$ or the palladium dimer $Pd_2(PBu^t_3)_4Br_2$.

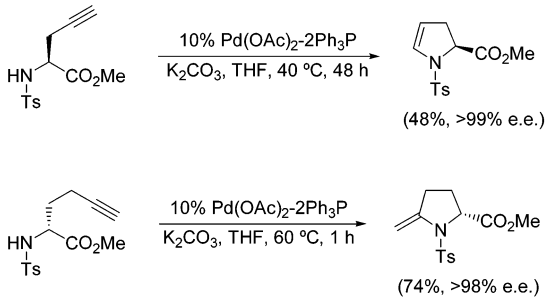
Better activity was observed for $[Pd(Triphos)](CF_3SO_3)_2$ also in the catalytic cyclization of aminoalkynes of general formula $RC{\equiv}C(CH_2)_nNH_2$ (R = H, Ph, *n* = 3; R = H, *n* = 4) and 2-(phenylethynyl)aniline at 111 °C.[77] Advantages of using this complex are the phosphine ligand that prevents the palladium complex from decomposition {$[Pd(MeCN)_4](BF_4)_2$ is very active but decomposes at high temperature} and the chemical inertness and good solubility provided by the triflate anion. Although TOFs are close to those observed with early-transition-metal catalysts, this catalyst showed higher tolerance toward poisons such as water and oxygen.

A remarkable increase in the reaction rate of cyclization of 6-aminohex-1-yne catalyzed by $[Pd(Triphos)](CF_3SO_3)_2$ was achieved by addition of triflic acid.[78] Several methods such as calorimetry, IR, and NMR spectroscopy brought out some evidence in concordance with the proposed catalytic cycle and with 2-methylidenepiperidine being the primary hydroamination product (Scheme 54).[79] According to the authors, a likely sequence would include the following: (a) initial coordination of the alkyne to the palladium center via the amine, (b) complex isomerization and coordination of the alkyne moiety to the metal center, (c) nucleophilic attack of the nitrogen lone pair giving a 2-ammonioalken-1-yl complex (the predominant palladium species in the catalytic mixture), and (d) protolytic cleavage of the Pd−C bond (the rate-determining step) leading to the product and regeneration of the catalyst. The protons coming from triflic acid seem to act as cocatalysts, accelerating the protolytic cleavage of the Pd−C bond in the intermediate complex.

Scheme 55



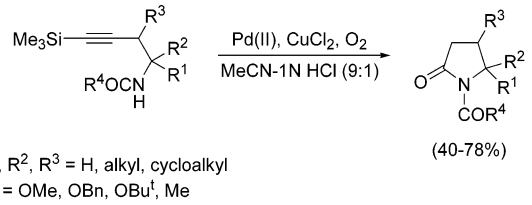
Scheme 56



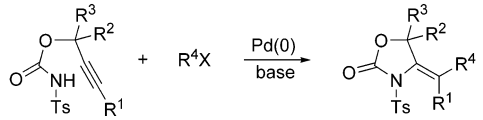
Alper et al. prepared a series of silica-immobilized palladium complexes from solutions of palladium(II) complexes and partially dehydroxylated silica. The catalytic activity of these materials was first tested in the cyclization of 6-aminohex-1-yne, higher conversions being found for those catalysts containing more basic ligands and those with more weakly coordinating anions.[80] Silica/*trans*-[PdMe(NO_3)(PMe_3)$_2$] showed the best behavior and was also used in the catalytic cyclization of 5-phenyl-4-pentyn-1-amine and 6-phenyl-5-hexyn-1-amine (Scheme 55). Reactions had to be performed at 90 °C since at room temperature they were extremely slow. In general, the reaction rates were comparable to or faster than those determined using early-transition-metal catalysts but significantly lower than those obtained by using lanthanide complexes. One main advantage of the catalysts is their stability (more than their molecular precursors) and reuse with little loss of activity.

Enantiomerically pure acetylene-containing α-amino acids were utilized by Rutjes et al. as versatile starting materials to accomplish the synthesis of various heterocycles promoted by palladium catalysts.[81] The cyclization reaction involves the carboxylate or amine functionality depending on the protecting group strategy applied, thus giving rise to a series of α-amino lactones and cyclic α-amino acid derivatives. For instance, the palladium-catalyzed cyclization of enantiopure *N*-tosyl propargylglycine methyl ester led to the expected five-membered endocyclic enamide (Scheme 56). The yield and enantiomeric excess of the product depended strongly on the nature of the base, solvent, palladium complex, and temperature, the best conditions to prevent racemization being those depicted in Scheme 56. The reaction, when applied to an enantiomerically pure homologous precursor, furnished the corresponding cyclic α-amino derivative containing an exocyclic carbon−carbon double bond, the yield being notably improved by the addition of iodobenzene. In the presence of aryl halides and vinyl triflates, similar palladium-catalyzed cyclizations occurred, giving the cross-coupled products without detectable racemization. It is worth noting that all cyclizations proceeded not only under palladium(II) catalysis but also with palladium(0)

Scheme 57



Scheme 58



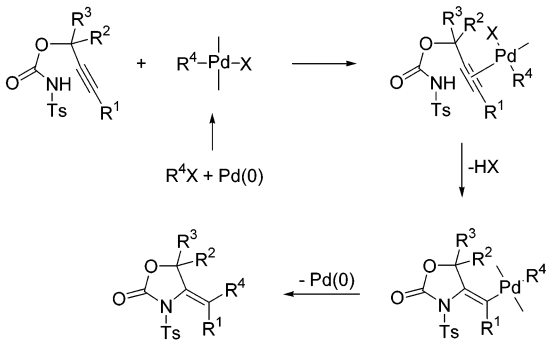
complexes, even in the absence of an aryl halide. In this case, the proposed catalytic cycle includes oxidative addition of Pd(0) into the N−H bond to form a Pd−H species, intramolecular insertion of the carbon−carbon triple bond generating a vinylpalladium species, and reductive elimination of the Pd−H intermediate.

The versatility of the palladium-catalyzed intramolecular hydroamination of alkynes has been demonstrated in the construction of other structurally very interesting heterocycles such as lactams, oxazolidinones, dipyrrins, pyrroles, and pyrazoles.[69c] For instance, Vatèle et al. reported the palladium(II)-catalyzed oxidative cyclization of diverse *N*-substituted aminoalkynes as a new route to the synthesis of γ-lactams.[82] *N*-Carbamoyl or *N*-acetyl aminoalkynes (but not *N*-benzyl derivatives) under Wacker-type conditions exhibited the appropriate nucleophilicity and basicity required for a successful cyclization, leading to the expected *N*-protected γ-lactams in moderate to good yields (Scheme 57). Very interesting spirocyclic γ-lactams were obtained in 71−78% yield when started from 1,1′-(cycloalkyl)aminoalkynes.

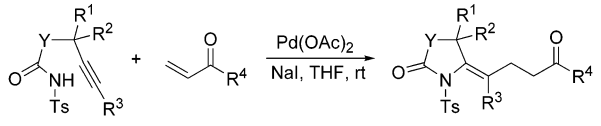
Arcadi[83] and Balme et al.[84] published at the same time the regio- and stereoselective synthesis of (*E*)-4-arylidene(alkenylidene)-3-tosyloxazolidin-2-ones through the palladium-catalyzed cyclization−coupling reaction of 2-propynyl tosylcarbamates with aryl iodides and vinyl triflates (Scheme 58). In Arcadi's report, the Pd(PPh_3)$_4$−K_2CO_3−DMF system at 60 °C was used for the coupling with aryl iodides, whereas addition of TBAC to that system was necessary for the coupling with vinyl triflates. In Balme's report, the optimum conditions employed included the use of Pd(OAc)$_2$ as the palladium source with the weakly coordinating ligand tri(2-furyl) phosphine, KOBu^t, and TEBA (benzyltriethylammonium chloride) in MeCN at 25 °C. In both cases, the origin of the (*E*)-selectivity observed was attributed to the *trans*-aminometalation across the carbon−carbon triple bond of the previously formed σ-palladium complex and reductive elimination of Pd(0) from the corresponding vinylpalladium complex (Scheme 59).

Lu et al. showed that the palladium(II)-catalyzed intramolecular aminopalladation of alkynes bearing carbamate, urea, or amido functionalities led to the corresponding vinylpalladium intermediates, which could be trapped by a Michael acceptor to furnish differently substituted oxazolidinones, imidazolidi-

Scheme 59



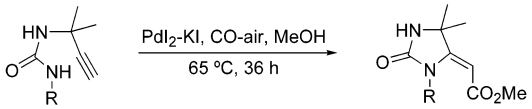
Scheme 60



(31-88%)

Y = O; R^1 = H, Me; R^2 = H, Me, Et, Ph, Pent^n; R^3 = H, Me; R^4 = H, Me
Y = NH, NBn; $R^1 = R^2 = R^3 = R^4$ = H
Y = CH_2; $R^1 = R^2 = R^3 = R^4$ = H

Scheme 61



(7-53%)

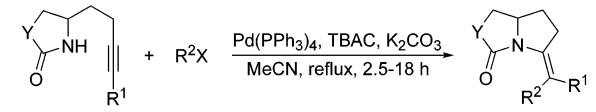
R = H, Pr^n, Bn, Ph, *p*-C_6H_4

nones, and lactams, respectively (Scheme 60).[85] This tandem alkyne aminopalladation−conjugate addition was proposed to take place through a mechanism involving (a) the activation of the carbon−carbon triple bond by palladium(II) species, followed by *trans*-attack of the tosyl amide to the coordinated carbon−carbon triple bond, generating an (*E*)-vinylpalladium species (aminopalladation), (b) insertion of the alkene, and (c) protonolysis of the newly formed carbon−palladium bond in the palladium enolate in the presence of halide ions.

A different stereochemical outcome was observed by Costa et al. when various acetylenic ureas were subjected to oxidative cyclization−alkoxycarbonylation in the presence of PdI_2–KI or Pd/C−KI as catalysts in MeOH under mild reaction conditions.[86] Cyclization occurred by *cis*-attack of the nitrogen atom on the carbon−carbon triple bond followed by stereospecific carbonylation, resulting in the corresponding oxazolidinones with (*Z*)-stereochemistry (Scheme 61). These oxazolidinones were obtained together with important amounts of the corresponding oxazolines, derived from a *trans*-attack of the carbonyl oxygen atom as a competing reaction.

Lactams and oxazolidinones bearing an alkyne moiety were subjected to a coupling−cyclization reaction with aryl halides and one vinyl bromide in the presence of $Pd(PPh_3)_4$ as a catalyst to yield the corresponding bicyclic enamides incorporating an aryl or vinyl group (Scheme 62).[87] It must be highlighted that the reaction takes place in a stereoselective manner, these groups being transferred syn

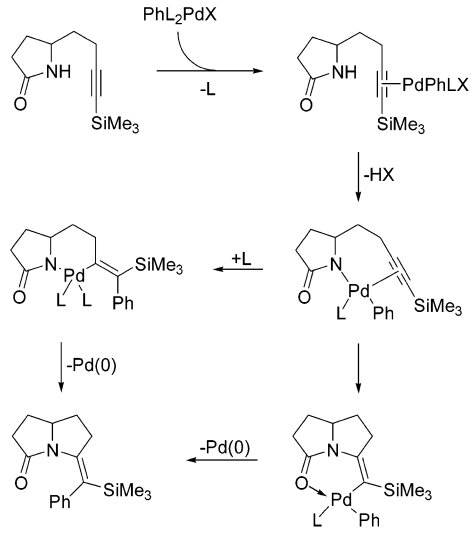
Scheme 62



(up to 78%)

R^1 = H, Me, TMS
R^2 = aryl, vinyl
Y = CH_2, O

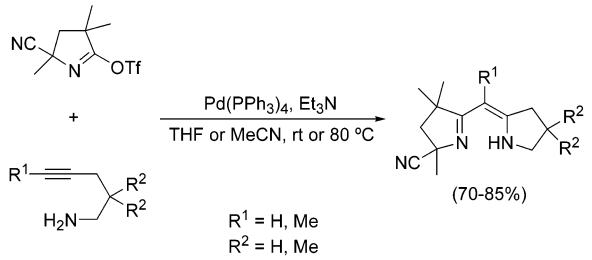
Scheme 63



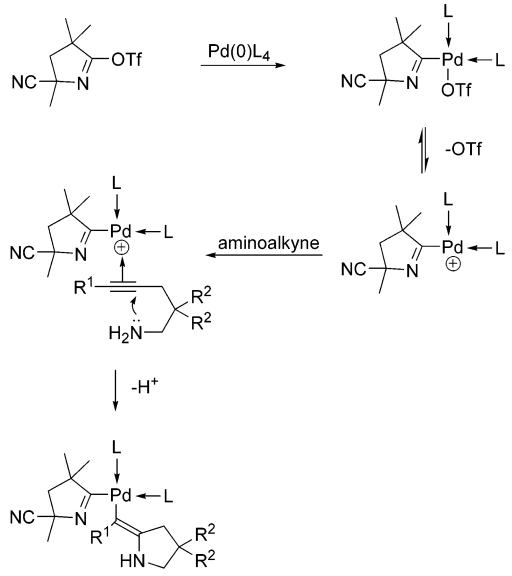
with respect to the nitrogen nucleophile onto the carbon−carbon triple bond, also in contrast with the above-mentioned Lu cyclization (Scheme 60). Within the aryl halides used for coupling, those substituted with electron-withdrawing groups showed a smooth cyclization (70%) whereas a very low yield was obtained with the electron-rich *p*-iodoanisole (<10%). To explain the stereoselectivity observed, a likely reaction pathway was proposed in concordance with some experimental results, which would start with a π-complex formation, followed by an intramolecular ligand exchange reaction giving a chelate. From this point, a carbopalladation or nitrogen ligand migration could occur, which after final reductive elimination would provide the product and the Pd(0) catalyst (Scheme 63). Thus, the coordination of the lactam nitrogen to the palladium could be essential for introduction of the organic part of the halide and the nitrogen nucleophile cis with respect to each other.

Jacobi et al. utilized the palladium(0)-initiated coupling−cyclization of triflates and alkynylamines as a key step in the synthesis of hexahydropyrrins and secocorrins.[88] Thus, (H_6)-dipyrrins were obtained from alkynylamines and an iminoyl triflate following a coupling−cyclization sequence using the general reagent system $Pd(PPh_3)_4$−Et_3N−THF (Scheme 64). This reaction seems to be very sensitive to steric effects, since direct nucleophilic displacement (leading to amidines) competes with the Pd(0)-initiated process when the geminal methyl groups are remote from the reacting center in the iminoyl triflate or the alkyne moiety is shielded by both terminal and adjacent methyl substituents. A detailed mechanistic study of this process led the authors to propose the following rationale: a *syn*-oxidative addition of Pd-

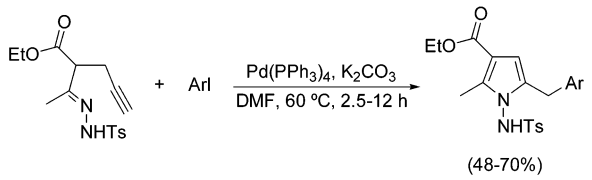
Scheme 64



Scheme 65



Scheme 66

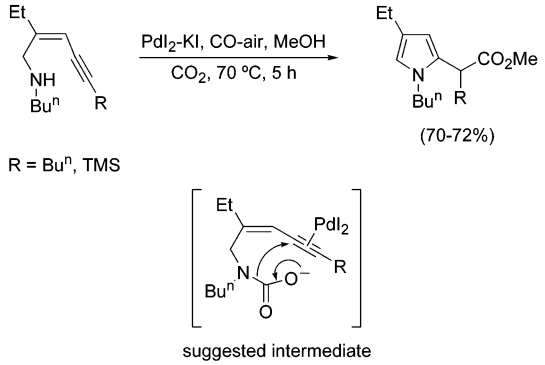


Ar = Ph, *m*-MeC_6H_4, *m*-ClC_6H_4, *m*-FC_6H_4, *m*-$CF_3C_6H_4$, *p*-ClC_6H_4, *p*-$MeCOC_6H_4$, *p*-$MeOCOC_6H_4$, *p*-$NO_2C_6H_4$, 1-naphthyl

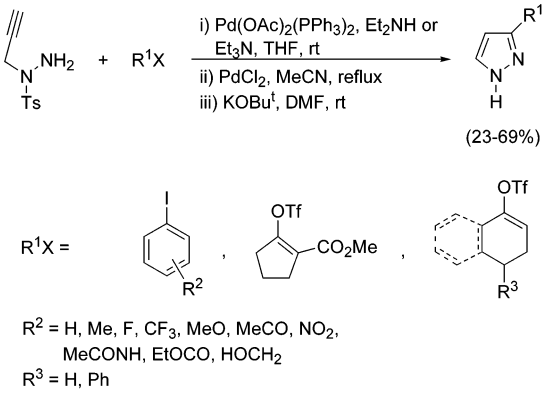
(0) to the iminoyl triflate would afford a square planar complex, followed by dissociation of the labile triflate ligand to give a cation. π-Complexation of this cation with the aminoalkyne would generate a cationic species highly activated toward nucleophilic attack. Finally, a *cis*-reductive elimination of the resulting σ-vinylpalladium complex and subsequent *E*,*Z*-equilibration would furnish the mentioned (H_6)-dipyrrins (Scheme 65).[89] This group also reported the cyclization−methoxycarbonylation of different acetylenic amides with the system $PdCl_2$−$CuCl_2$−CO−MeOH to afford moderate to excellent yields of stable enamide esters.[90]

Substituted pyrroles were obtained in moderate yields by the palladium-catalyzed reaction of ethyl 2-acetyl-4-pentynoate tosylhydrazone with aryl iodides in the presence of potassium carbonate (Scheme 66).[91] A mechanism similar to that depicted in Scheme 59 was suggested to account for the formation of the products. Using $Pd(OAc)_2$ and P(*o*-Tol)$_3$ as the catalytic system under a carbon monoxide atmosphere, a domino reaction occurred with incorporation of an arylcarbonylmethyl substituent onto the pyrrole ring.

Scheme 67



Scheme 68

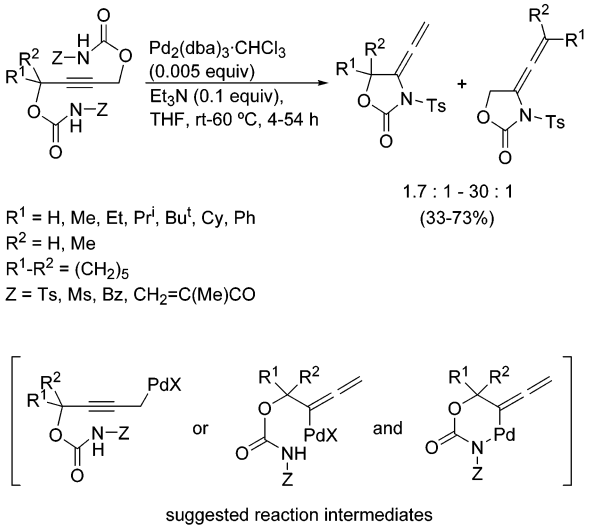


More recently, Gabriele, Salerno et al. discovered the crucial effect of carbon dioxide in promoting the PdI_2−KI-catalyzed oxidative cyclization−alkoxycarbonylation of (*Z*)-(2-en-4-ynyl)amines leading to methyl 2-(pyrrol-2-yl)acetates.[92] Apparently, in the absence of CO_2, reoxidation of Pd(0) by I_2 (formed by oxidation of the HI released with oxygen) is inhibited by protonation of the substrate with HI. However, in the presence of CO_2, the cyclization−alkoxycarbonylation occurs through the less basic carbamate species, leaving free HI available for Pd(0) reoxidation, the CO_2 being eliminated during the cyclization process (Scheme 67).

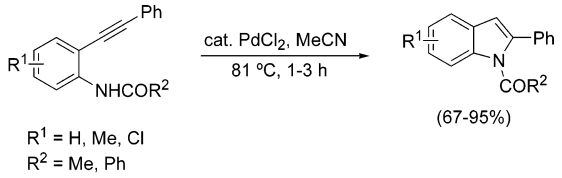
Cacchi et al. described a straightforward synthesis of functionalized pyrazoles, based on the palladium-catalyzed coupling of *N*-tosyl-*N*-propargylhydrazine with aryl halides or vinyl triflates, followed by palladium-catalyzed intramolecular hydroamination and *p*-toluenesulfinic acid elimination (Scheme 68).[93] The key cyclization step was effected under Utimoto's reaction conditions ($PdCl_2$, MeCN, reflux), the expected products being obtained mostly in moderate yields but in a one-pot procedure.

In a different mechanistic context, the palladium-catalyzed aminocyclization of 2-butyn-1,4-diol biscarbamates reported by Tamaru et al. can be included, which allows the synthesis of 4-ethenylidene-2-oxazolidinones in moderate to good yields (Scheme 69).[94] The presence of substituents at the C1-carbon atom of the starting 2-butyn-1,4-diol biscarbamates led to a mixture of regioisomers, the major one bearing the substituents on the C5-carbon atom of

Scheme 69



Scheme 70



the oxazolidinone ring. The reaction was suggested to proceed by oxidative addition of Pd(0) species to one of the C−O carbamate bonds, generating a propargylpalladium and/or allenylpalladium intermediate. The former could cyclize in a S_N2' fashion, whereas the latter could suffer reductive elimination through the corresponding azapalladacycle.

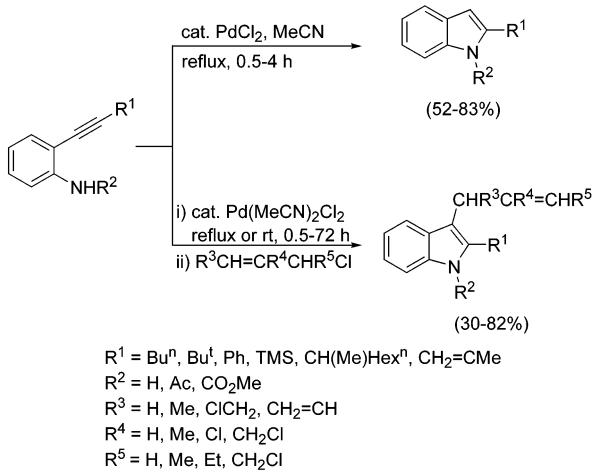
The continuous interest of synthetic organic chemists in the synthesis of benzene-condensed heteroaromatic compounds is well known, in particular toward the synthesis of indoles.[69d,e,95] Besides the well-known classical methods for indole synthesis, those involving intramolecular cyclization of 2-alkynylanilines as starting materials offer straightforward access to the indole moiety. This cyclization has been mainly achieved in the presence of a base,[96] TBAF[97] or polymer-supported fluoride,[98] or under palladium catalyst promotion.[69]

It was in the mid 1980s when Taylor et al. applied Utimoto's methodology[73a] to induce the intramolecular cyclization of a series of 2-acetamidotolanes, giving the corresponding indoles in good to excellent yields (Scheme 70).[99] A mechanism similar to that previously proposed by Utimoto et al. was suggested.

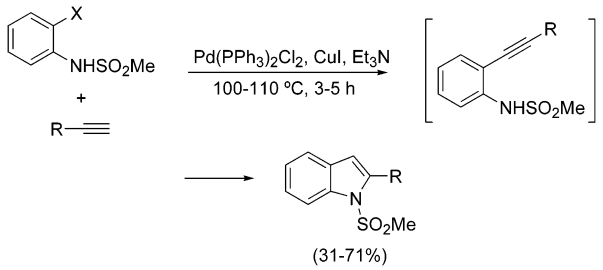
Utimoto et al. described the aminopalladation of *N*-substituted-2-alkynylaniline derivatives with a catalytic amount of $PdCl_2$, the intermediate 3-indolylpalladium species leading to the corresponding indoles (Scheme 71).[100] When this intermediate was allowed to react with allyl chlorides, under the catalytic action of $Pd(MeCN)_2Cl_2$, and in the presence of methyloxirane (as a proton scavenger), a regioselective attack at the γ-position of the allyl halide occurred, affording a variety of *N*-substituted-3-allyl-2-alkylindoles (Scheme 71).

Almost parallel and in a work very close to that by Utimoto et al., Stille et al. reported the $Pd(MeCN)_2Cl_2$-

Scheme 71



Scheme 72

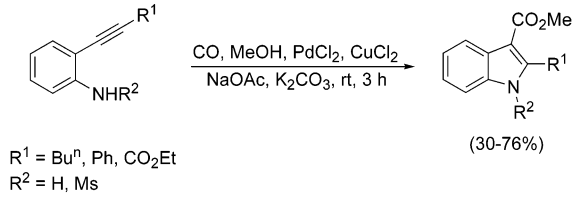


catalyzed intramolecular cyclization of *N*-acetyl-2-alkynylanilines in MeCN at 80 °C.[101] A wide range of substituents on the alkyne moiety [Pr^n, Pr^i, Bu^n, Ph, $(CH_2)_2$OTBDMS, $(CH_2)_3$OTBDMS, $(CH_2)_4C\equiv$CTMS] and on the aromatic aniline ring (5-Me, 5-Cl, 5-OTf, 6-OMe, 6-CO_2Me) were tested and tolerated under the reaction conditions. Yields were obtained within the range 34−82% in relatively short reaction times (0.5−4 h).

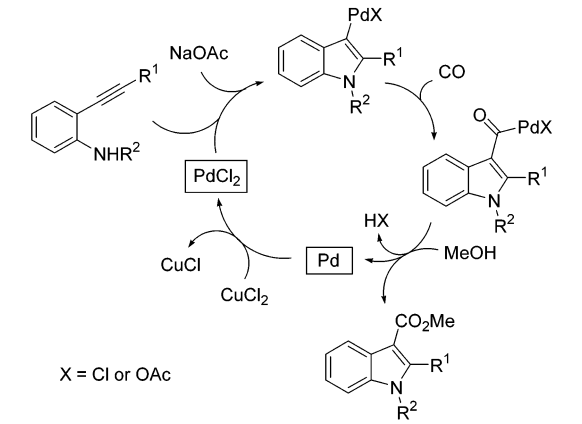
There are several research groups whose efforts and contributions to develop effective palladium-catalyzed synthesis of indoles from 2-alkynylaniline derivatives are worth noting. For instance, Yamanaka, Sakamoto et al. reported in 1988 the one-step synthesis of 1-methylsufonylindoles by reacting *N*-(2-bromophenyl)- and *N*-(2-iodophenyl)methanesulfonamide with terminal alkynes in the presence of $Pd(PPh_3)_2Cl_2$ and CuI (Scheme 72).[102] Despite the relatively harsh reaction conditions needed (100−110 °C in a sealed tube), this reaction found application even for terminal alkynes bearing different functional groups. The presence of CuI seemed to be essential, a possible cooperative action of CuI and $Pd(PPh_3)_2Cl_2$ driving the cyclization step.

When the above reaction was performed in the presence of carbon monoxide and methanol under basic conditions, a sequential cyclization−carbonylation occurred, giving rise to methyl indole-3-carboxylates (Scheme 73).[103] Starting from 2-alkynylbenzamides, the corresponding 3-alkylideneisoindoles were obtained in low to moderate yields. A catalytic cycle was proposed in which the indolylpalladium complex, resulting from the reaction of ethynyl-

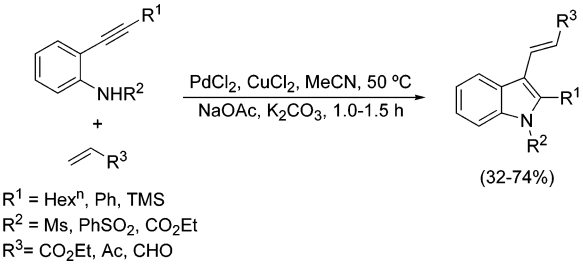
Scheme 73



Scheme 74



Scheme 75

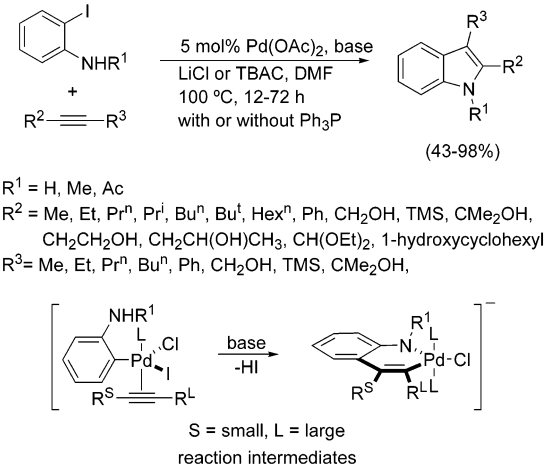


anilines and palladium(II) chloride, reacts with carbon monoxide to form indolylacylpalladium species. Reaction of the latter with methanol would lead to the final products, palladium(II) chloride being regenerated by oxidation of the palladium(0) species with copper(II) chloride (Scheme 74).

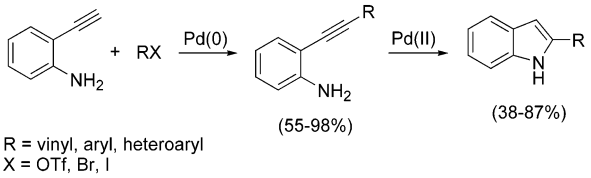
Cross-coupling of the above-mentioned indolylpalladium species with electron-deficient alkenes (Heck reaction) gave 2-substituted 3-alkenylindoles. The cyclization−alkenylation reaction proceeds fast under mild reaction conditions and in moderate yields (Scheme 75).[104] Alternatively, the reaction was performed with $PdCl_2$, $CuCl_2 \cdot 2H_2O$, and TBAF in THF under reflux.[105]

Larock et al. reported the palladium-catalyzed coupling−cyclization of 2-iodoaniline and its *N*-methyl, acetyl, and tosyl derivatives with a wide range of internal alkynes to furnish 2,3-disubstituted indoles in good to excellent yields.[106] The best results were obtained by utilizing an excess of the alkyne in the presence of catalytic palladium(II) acetate, sodium or potassium acetate, lithium chloride or TBAC, and with occasional addition of triphenylphosphine (Scheme 76). The annulation of unsymmetrically substituted alkynes proved to be regioselective, the more sterically bulky group accommodated nearer the nitrogen atom in the indole product. It is noteworthy that a wide variety of silylated alkynes could

Scheme 76



Scheme 77

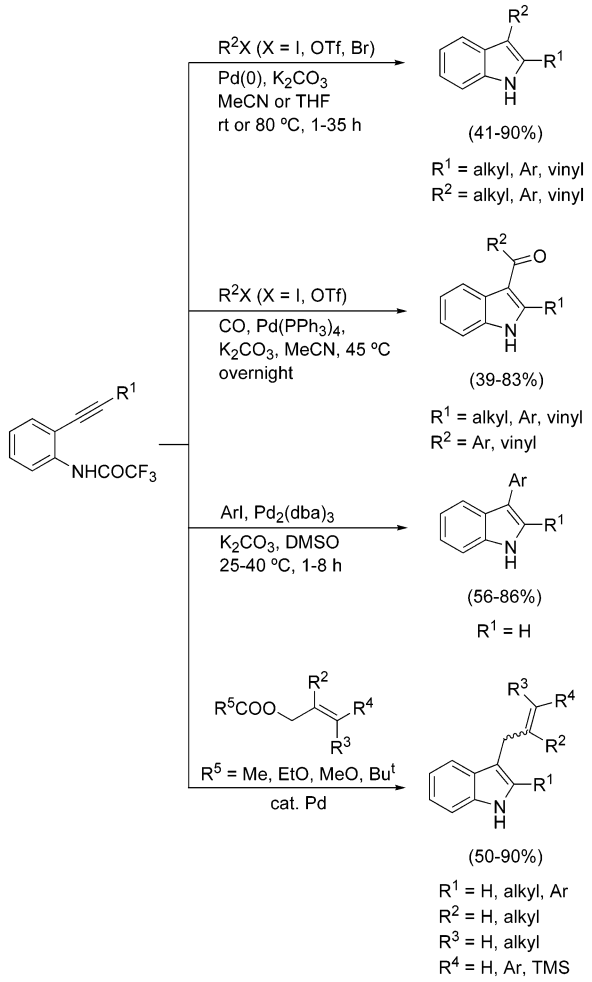


be employed in this annulation process with no apparent desilylation, the resulting silyl-substituted indoles being versatile materials for the synthesis of other substituted indoles. A pronounced directing effect, probably due to coordination with palladium, explained the regiochemistry observed in the insertion step of alkynes bearing hydroxy groups.

The above-mentioned whole indole synthesis was suggested to proceed via (a) reduction of $Pd(OAc)_2$ to Pd(0), (b) coordination of the chloride anion to form a chloride-ligated zerovalent palladium species, (c) oxidative addition of the aryl iodide to Pd(0), (d) coordination of the alkyne to the palladium atom of the resulting arylpalladium intermediate and subsequent regioselective *syn*-insertion into the arylpalladium bond, (e) nitrogen displacement of the halide in the resulting vinylic palladium intermediate forming a six-membered heteroatom-containing palladacycle, and (f) reductive elimination to form the indole and regeneration of Pd(0).

Cacchi et al. also contributed outstandingly to the field of the palladium-catalyzed synthesis of indoles from 2-alkynylaniline derivatives. In one of the earlier reports, this group described an indole synthesis methodology consisting in the palladium-catalyzed coupling of 2-ethynylaniline with aryl and vinyl triflates [$Pd(PPh_3)_4$, CuI, Et_2NH, rt, 3−5 h], affording 2-alkynyl- and 2-arylethynylanilines, followed by $PdCl_2$-catalyzed intramolecular hydroamination ($PdCl_2$, MeCN, 70 °C, 2.5−9.0 h).[107] In general, good yields were obtained, only 2-arylethynylanilines containing electron-withdrawing groups near or conjugated with the acetylenic moiety producing the indole product in moderate yield (Scheme 77). Alternatively, comparable or higher yields were obtained when the cyclization step was accomplished with the $PdCl_2$−TBAC combination under an acidic CH_2Cl_2−HCl two-phase system at room temperature.[108] How-

Scheme 78

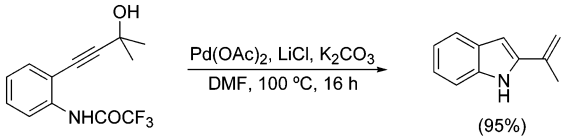


ever, the use of neutral conditions was found to afford better results for 2-alkynylanilines containing electron-withdrawing groups on the alkyne moiety.

Further research by the above group has focused on the synthesis of differently substituted indoles using 2-alkynyltrifluoroacetanilides as starting materials. For instance, 2,3-disubstituted indoles were obtained by palladium-catalyzed heteroannulation of 2-alkynyltrifluoroacetanilides in the presence of vinyl triflates or aryl halides[109] and with ethyl iodoacetate or benzyl bromide (Scheme 78).[110] The notion that the acidity of the nitrogen−hydrogen bond is an important feature of this heteroannulation was supported by the fact that no indoles were obtained using aniline derivatives containing a free amino group or an acetamido group. In contrast, a dramatic change was observed in the reactivity of the aniline moiety in the presence of an electron-withdrawing group as strong as the trifluoroacetyl group. The authors proposed a mechanism involving a Wacker-type activation of the carbon−carbon triple bond by RPdX species followed by cyclization.

When the above reaction was performed under a carbon monoxide atmosphere (1 or 7 atm) and in the presence of potassium carbonate, 2-substituted 3-acyl indoles were produced in fair to good yields (Scheme 78).[111] With aryl iodides containing electron-withdrawing groups, anhydrous acetonitrile and a higher pressure of CO was needed. This cyclization reaction

Scheme 79



was rationalized according to a sequence involving (a) the oxidative addition of the aryl halide or vinyl triflate to Pd(0) followed by (b) carbonylation to give a σ-acylpalladium intermediate R^2COPdX, (c) generation of a π-alkynylpalladium complex, (d) intramolecular attack of the nitrogen anion on the carbon−carbon triple bond, and (e) reductive elimination with regeneration of a Pd(0) species. Some other mechanisms involving carbonylation from an indolylpalladium intermediate or alkyne insertion into the CO−Pd bond in the π-alkynylpalladium complex were not ruled out. This methodology was applied to the synthesis of the analgesic pravadoline. When *o*-(*o*′-aminophenylethynyl)trifluoroacetanilide was used as the starting material, the palladium-catalyzed carbonylative cyclization with aryl iodides followed by cyclization of the resulting 3-acylindoles, allowed the preparation of 6-aryl-11*H*-indolo[3,2-*c*]-quinolines in 35−86% yield as a one-pot process.[112]

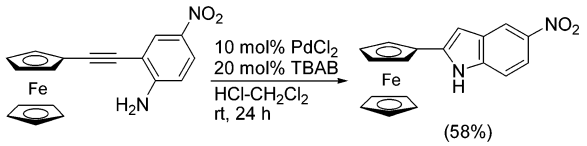
3-Aryl-2-unsubstituted indoles could be prepared by the palladium-catalyzed reaction of 2-ethynyltrifluoroacetanilide with a series of aryl iodides (Scheme 78).[113] The system composed of $Pd_2(dba)_3$, DMSO, and K_2CO_3 showed the best results for aryl iodides bearing both electron-withdrawing and electron-donating substituents. 2-Ethynyltrifluoroacetanilide subjected to the same reaction conditions in the absence of aryl iodides afforded indole in 80% yield.

Finally, the reaction of 2-alkynyltrifluoroacetanilides with allyl esters provided a straightforward synthesis of 3-allylindoles (Scheme 78).[114] Three different procedures were designed for the construction of the 3-allylindole structure including (a) stepwise palladium-catalyzed *N*-allylation of 2-alkynyltrifluoroacetanilides and its subsequent cyclization, (b) a one-pot procedure without isolating the *N*-allyl derivative, and (c) a procedure likely not involving the *N*-allyl derivative. The reactions carried out in the presence of the electron-rich sterically encumbered ligand tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp) exhibited high regioselectivity, the indolyl moiety bound mainly to the less substituted allyl terminus. The partial loss of the olefin geometry seems to be the only limitation of this methodology.

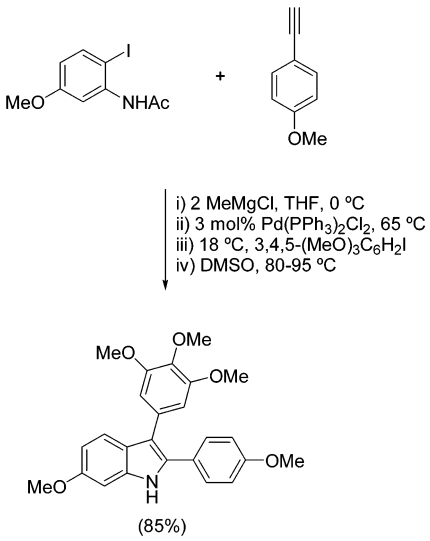
2-[(3-Hydroxy-3,3-dimethyl)prop-1-ynyl]trifluoroacetanilide was transformed into 2-(1-methylethenyl)indole by palladium(II)-catalyzed cyclization in DMF at 100 °C for 16 h. A reaction mechanism was proposed in which dehydration from a vinyl palladium species took place (Scheme 79).[115]

More recently, a ferrocenyl aryl acetylene, obtained in 96% by the Sonogashira−Heck−Cassar reaction of ferrocenylacetylene and 2-iodo-3-nitroaniline [$Pd(PPh_3)_2Cl_2$−CuI−Et_3N, 90 °C, 4 h], was subjected to annulation in the presence of $PdCl_2$ and TBAB in a biphasic system (HCl−CH_2Cl_2 1:1), leading to 2-ferrocenyl-5-nitroindole in 58% yield (Scheme 80). Un-

Scheme 80



Scheme 81



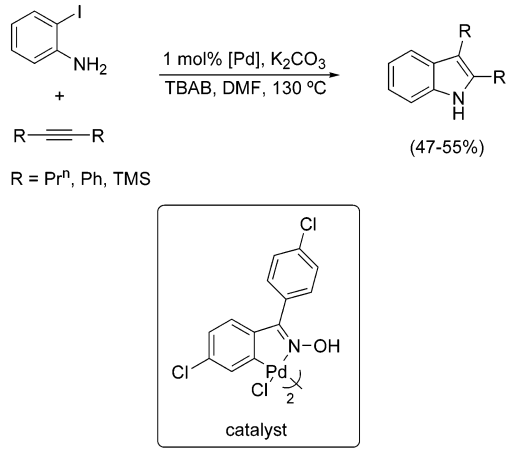
fortunately, a 23% yield of ferrocenylacetylene was also isolated.[116]

A palladium-mediated one-pot, multicomponent coupling process was described by Flynn et al. as direct access to 2,3-disubstituted benzo[*b*]furans and indoles.[117] The methodology described in this preliminary communication, though mainly applied to the synthesis of benzo[*b*]furans, also includes the synthesis of a 2,3-disubstituted indole. The procedure utilized involves initial deprotonation of a mixture of an *o*-iodoacetanilide derivative and a terminal acetylene with 2 equiv of MeMgCl at 0 °C, addition of $Pd(PPh_3)_2Cl_2$ and heating at 65 °C to give the coupling product, and final dilution with DMSO and addition of an aryl iodide followed by heating (Scheme 81). Some indole analogues were synthesized from an *o*-iodotrifluoroacetanilide derivative in combination with a carbonylation reaction and other aryl acetylenes.[118] These products, structurally related to some cytotoxic 2,3-diarylindole systems, showed moderate to poor activity both as tubulin polymerization inhibitors and as cytotoxins.

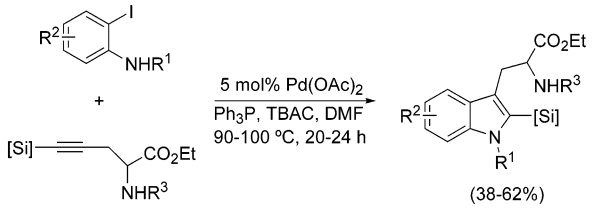
Nájera et al. reported the first synthesis of indoles from *o*-iodoaniline and internal alkynes catalyzed by a palladacycle.[119] An oxime-derived, chloro-bridged palladacycle was used as catalyst, which was shown to be thermally stable, not sensitive to air or moisture, and easily accessible from inexpensive starting materials. The coupling−cyclization process was exclusively applied to symmetrically substituted internal alkynes giving the corresponding indoles in moderate isolated yields (Scheme 82).

The palladium-catalyzed construction of indole systems from 2-alkynylaniline derivatives has also demonstrated its usefulness as the key step in the total synthesis of some naturally occurring compounds or related structures. For instance, Gronowitz et al. prepared a variety of tryptophans through a strategy that involved the palladium-catalyzed coupling−annulation of *o*-iodoanilines and silylated acetylenes followed by desilylation. Yields were moderate for the intermediate silylated indoles (38−62%) but low, in general, for the desilylated products (13−64%) (Scheme 83).[120]

Scheme 82



Scheme 83



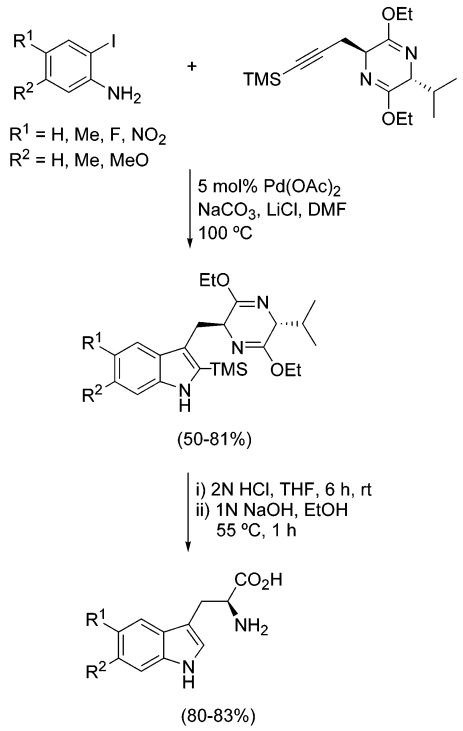
R1 = H, Ac, Boc
R2 = H, 4-Br, 4-Cl, 4-F, 4-NO2, 4-NH2, 5-NO2
[Si] = TMS, TBDMS

The asymmetric version of this tryptophan synthesis strategy was reported by Cook et al., the chiral fragment being provided by a propargyl-substituted bislactim ethyl ether derived from Schöllkopf's chiral auxiliary (Scheme 84).[121] The efficiency of this indole ring formation was demonstrated in a 300-g-scale preparation of a tryptophan derivative that was utilized as a precursor for the synthesis of the alkoxy-substituted indole bases 16-*epi*-N_a-methylgardneral, 11-methoxyaffinisine, and 11-methoxymacroline as well as the indole alkaloids alstophylline and macralstonine.[122]

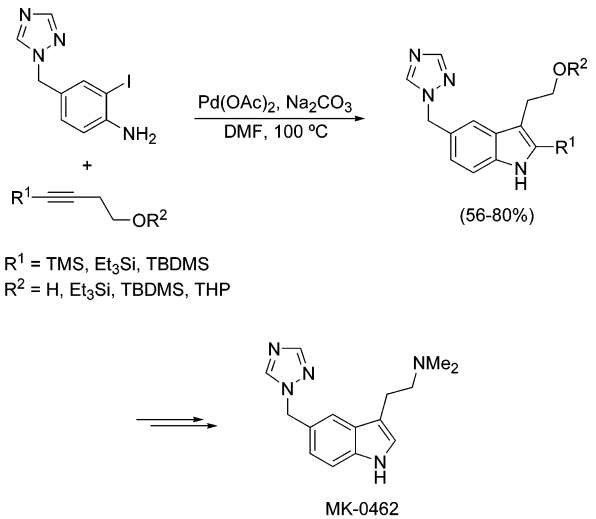
Chen et al. disclosed a highly efficient synthesis of the dimethyltryptamine MK-0462, a potential antimigraine drug, based on the palladium-catalyzed coupling and cyclization between (4-amino-3-iodobenzyl)-1*H*-1,2,4-triazole and silylated alkynes. The use of silyl protection at the terminal carbon atom of the acetylene was recommended in order to prevent homocoupling, although protection of the hydroxy group also played an important role in the coupling step (Scheme 85).[123]

Saulnier et al. accomplished the synthesis of a rebeccamycin-related indolo[2,3-*a*]carbazole by a palladium(0)-catalyzed polyannulation reaction, where four bonds were formed in a single step from a

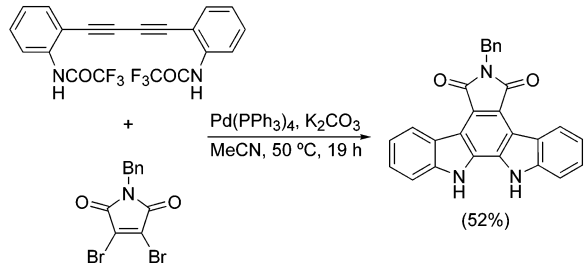
Scheme 84



Scheme 85



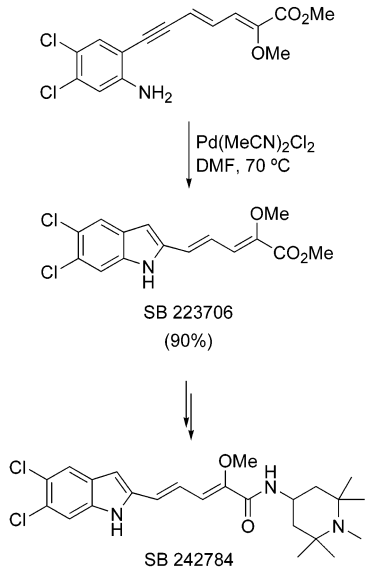
Scheme 86



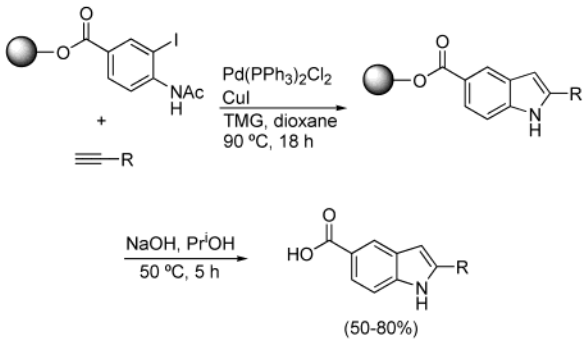
symmetrical 1,3-diacetylene and 3,4-dibromomaleimide (Scheme 86).[124]

2-Dienylindole SB 242784, a compound developed to treat osteoporosis, was elegantly synthesized by Yu et al. utilizing a palladium-catalyzed three-component coupling reaction followed by intramolecular cyclization.[125] The ynediene resulting from

Scheme 87



Scheme 88

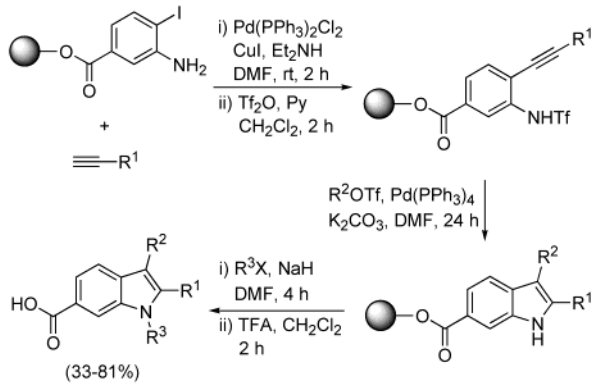


the consecutive Castro-Stephens and Suzuki couplings cyclized under $Pd(MeCN)_2Cl_2$ catalysis to afford the indole SB 223706, an immediate precursor of SB 242784 (Scheme 87).

In recent years and parallel to the development of the solid-phase synthesis, several research groups have shown great interest in applying this powerful synthetic tool to the obtention of indoles under the promotion of palladium catalysts. For instance, Bedeschi et al. reported the one-pot solid-phase synthesis of 2-substituted indoles by the coupling−cyclization reaction of 2-iodoaniline derivatives and terminal alkynes, catalyzed by the Pd(0)−Cu(I) system (Scheme 88).[126] The presence of tetramethylguanidine (TMG) seems to be essential to effect the coupling−cyclization steps in one pot. The expected indoles were obtained in 50−80% overall yield after cleavage of the TentaGel-S resin in basic medium.

Trisubstituted indoles were obtained by Ellingboe et al. through a solid-phase synthesis pathway involving three independently variable components.[127] 3-Amino-4-iodobenzoic acid was attached to a modified Wang resin and subjected to Sonogashira coupling with a wide range of terminal alkynes (the first component), followed by trifluoroacetylation. Palladium-catalyzed cyclization of the resulting resin in the presence of a vinyl triflate (the second component) led to 2,3-disubstituted indole derivatives. The *N*-

Scheme 89



R^1 = Bu^n, *c*-C_5H_9, Ph, $PhCH_2CH_2$, *m*-$MeOCOC_6H_4O(CH_2)_3$, *p*-$C_6H_4CON(Me)CH_2$
R^2 = 1-cycloalkenyl
R^3X = MeI, $BrCH_2CO_2Et$

Scheme 90

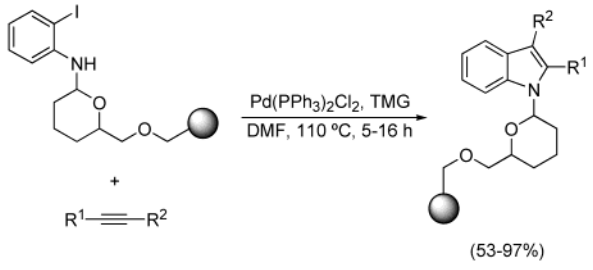
R^1 = H, Ac, Me_2CHCO
R^2 = Me, Pr^n, Ph, CO_2Et, $HO(CH_2)_2$, *m*-$MeOC_6H_4(CH_2)_2$, $(CH_2)_4NCH_2$
R^3 = Pr^n, Bu^t, Ph, TMS, $(CH_2)_4NCH_2$

alkylation with reactive alkylation agents, such as benzyl halides or bromoacetates, introduced the third component, and final cleavage of the resin released the corresponding 1,2,3-trisubstituted indoles in moderate to good yields (Scheme 89).

Zhang et al. also developed an efficient solid-phase synthesis of trisubstituted indoles based on the palladium-mediated heteroannulation of internal alkynes with resin-bound *o*-iodoaniline derivatives.[128] Rink amide AM resin was utilized in this case to support the *o*-iodoaniline derivatives, which by reaction with internal alkynes in the presence of a catalytic amount of $Pd(OAc)_2$, Ph_3P, LiCl (or TBAC for silylalkynes), a base (K_2CO_3, Na_2CO_3, or KOAc), in DMF at 80 °C, followed by resin cleavage with TFA−CH_2Cl_2 furnished the indole systems in good to excellent yields (Scheme 90). The process was highly regioselective, with insertion of the intermediate arylpalladium species preferably occurring into the alkyne from the less hindered side. The method was compatible with a variety of functionalities on the alkyne such as alkyl, aryl, silyl, hydroxy, methoxy, amino, and ester. Moreover, the heteroannulation with trimethylsilylalkynes afforded very versatile resin-bound precursors of 2-unsubstituted or other 2-substituted indole derivatives. Berteina-Raboin et al. applied this methodology, in association with microwave irradiation, to the solid-phase synthesis of 5-carboxamido-*N*-acetyltryptamine.[129]

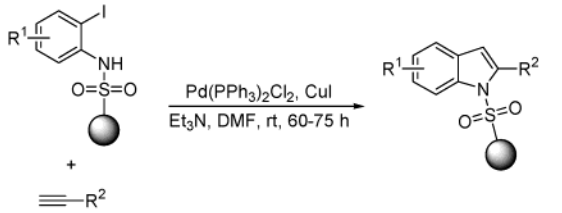
The above methodology, but starting from *N*-mesyl resin-bound *o*-iodoaniline derivatives, was also applied to the heteroannulation of terminal alkynes, affording the corresponding 2-substituted indoles in

Scheme 91



R^1 = Pr^n, Bu^t, Ph, TMS
R^2 = Me, Et, Pr^n, Ph, CH_2CH_2OH

Scheme 92



R^1 = H, 6-F, 6-MeO, 5-CO_2Me
R^2 = Bu^n, Ph, $MeOCH_2$, $PhSCH_2$, $HO(CH_2)_2$, $(EtO)_2CH$, *p*-MeC_6H_4, *p*-FC_6H_4, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$, 2-pyridyl, 6-MeO-2-naphthyl

much better yields (76−94%) than those obtained for the solution-phase synthesis.[130] The resin-bound 2-substituted indoles were further subjected to the Mannich reaction, giving, after resin cleavage, 2-substituted-3-aminomethyl indoles with good yields and high purities.

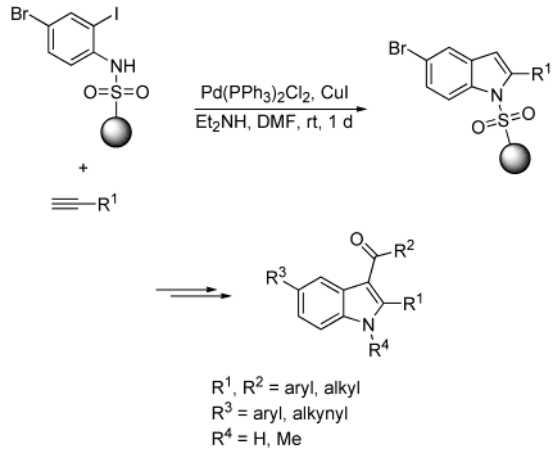
Smith et al. developed an efficient method for the traceless solid-phase[131] synthesis of 2,3-disubstituted indoles using a THP linker and a Pd(0)-mediated annulation of 2-iodoaniline and internal acetylenes (Scheme 91).[132] The best results were obtained by using $Pd(PPh_3)_2Cl_2$ as catalyst and TMG as base, resin cleavage with 10% TFA providing the free indole products in moderated to excellent yields.

Zhang's group reported the solid-phase palladium-mediated construction of indole derivatives based on a traceless, activating sulfonyl linker.[133] The presence of this strong electron-withdrawing sulfonyl linker allowed proper activation of the amino group, both the coupling and indole cyclization occurring in one pot under relatively mild conditions. Good to excellent yields were obtained after cleavage of the sulfonamide linkage (TBAF, THF, 70 °C, 5 h), irrespective of the electron-donating or electron-withdrawing character of the substituent on the 2-iodoaniline derivative (Scheme 92).

Similarly, 2,3,5-trisubstituted indoles were synthesized by Schultz et al. in three steps starting from a PS-sulfonyl resin-bound *o*-iodoaniline.[134] The key step for the construction of the indole ring was the palladium-mediated coupling−cyclization of the resin-bound sulfonamide with terminal alkynes (Scheme 93). The resin-bound indoles were very versatile substrates that were subjected to acylation at C-3 and to Sonogashira or Suzuki couplings at C-5. Additionally, *N*-methylation also could be effected after resin cleavage.

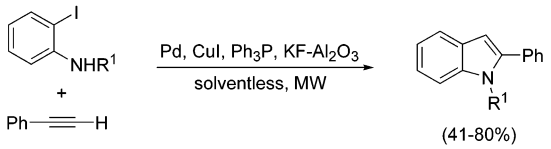
A solventless, microwave-enhanced synthesis of 2-substituted indoles was reported by Kabalka et al.

Scheme 93



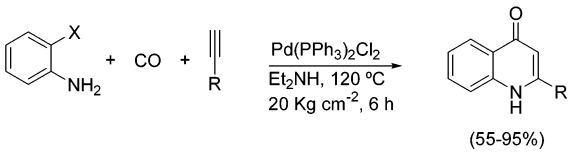
R^1, R^2 = aryl, alkyl
R^3 = aryl, alkynyl
R^4 = H, Me

Scheme 94



R^1 = COMe, SO_2Me

Scheme 95

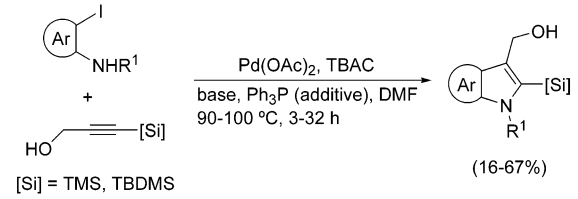


X = I, Br
R = Ph, *p*-$MeOC_6H_4$, *p*-$EtOCOC_6H_4$, 3,4-$(OCH_2O)C_6H_3$, Hex^n, CH_2OTHP, CMe_2OTHP, $(CH_2)_3OAc$, $(CH_2)_3CO_2Me$

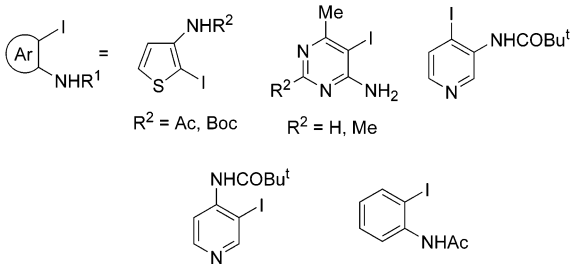
based on the one-pot Sonogashira coupling−cyclization reaction of *o*-iodoaniline derivatives and terminal aryl-substituted alkynes, carried out on potassium fluoride doped with alumina in the presence of palladium powder, copper(I) iodide, and triphenylphosphine (Scheme 94).[135] *o*-Iodoaniline itself led exclusively to the coupling product or mixtures of the coupling and cyclized products, the best results being obtained for some *o*-iodoaniline derivatives bearing an electron-withdrawing group on the nitrogen atom. Improved yield of the indoles was observed in the presence of additional palladium(II).

Besides indoles, many other different heterocondensed compounds have been synthesized by palladium-catalyzed cyclization of 1-amino-2-alkynylaryl and hetaryl derivatives. In most cases in which those derivatives were prepared by coupling of a 1-amino-2-haloarene (or heteroarene) with an alkyne, spontaneous cyclization occurred under the reaction conditions. For instance, in the early 1990s Torii et al. reported the palladium-catalyzed carbonylation of 2-haloaniline in the presence of terminal alkynes under a CO atmosphere, providing a variety of 2-substituted-4-quinolones (Scheme 95).[136] The reaction of the arylacetylenes was shown to give better yields than those of the aliphatic acetylenes. Better yield was also observed for 2-iodoaniline in comparison with 2-bromoaniline.

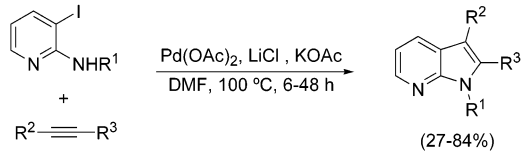
Scheme 96



[Si] = TMS, TBDMS



Scheme 97



R^1 = H, Me, Bn, *p*-$MeOC_6H_4CH_2$
R^2 = Pr^n, Ph, TMS
R^3 = Me, Pr^n, Ph, CH_2OH, CH_2CH_2OH

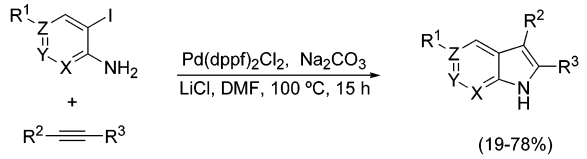
The same reaction was reported by Kalinin et al. but exclusively applied to terminal arylacetylenes and using Pd(dppf)Cl_2 as catalyst. The expected 2-aryl-4-quinolones were obtained in 62−84% yield. It is worth noting that even $PdCl_2$ showed significant catalytic activity.[137]

Gronowitz et al. described the palladium-catalyzed synthesis of several heterocondensed pyrroles from 1-amino-2-iodohetaryl derivatives and trialkylsilyl propargyl alcohols.[138] Thiophene, pyrimidine, pyridine, and *o*-iodoaniline derivatives were used as substrates, the corresponding products being obtained in rather low to moderate yields under different base combinations (Scheme 96).

An efficient approach to the synthesis of 7-azaindoles involved the palladium-catalyzed heteroannulation of internal alkynes with 2-amino-3-iodopyridine derivatives (Scheme 97).[139] The system $Pd(OAc)_2$−LiCl−KOAc−DMF exhibited the best results, unsymmetrical alkynes giving rise regioselectively to 2,3-disubstituted-7-azaindoles with the bulkier groups ending up nearer the nitrogen atom. Again, the 2-silylated products were very valuable precursors of other 2-substituted-7-azaindoles accessible by protonolysis, halogenation, or coupling reaction.

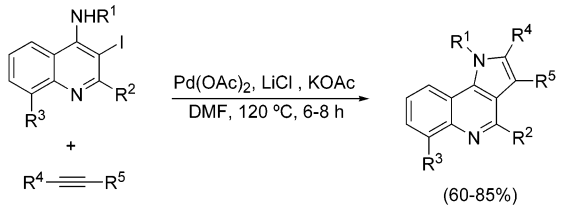
Ujjainwalla et al. discovered that Pd(dppf)Cl_2 was a superior catalyst to $Pd(OAc)_2$ for the above transformation, the presence of LiCl being essential to get good regioselectivity, reproducibility, and improved yields.[140] Under these reaction conditions, 2,3,5-trisubstituted indoles were obtained with good tolerance of the functional groups at C-5 of the 2-amino-3-iodopyridine precursor. This methodology was extended to the synthesis of 2,3-disubstituted-6-azaindoles and 2,3-disubstituted-5-azaindoles, which

Scheme 98



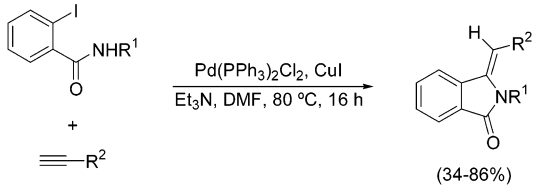
X = N; Y = CH; Z = C; R^1 = H, Me, Cl, CO_2Me
X = CH; Y = N; Z = C; R^1 = H
X = Y = CH; Z = N
R^2 = H, Pr^n, Ph, $(CH_2)_2OH$
R^3 = Pr^n, Ph, TMS, Et_3Si

Scheme 99



R^1 = Bu^n, Bn, *o*-MeC_6H_4, 4-MeO-2-MeC_6H_3
R^2 = H, Me
R^3 = OMe, OCF_3
R^4 = Pr^n, Ph, TMS
R^5 = Me, Pr^n, CH_2OH, CH_2CH_2OH

Scheme 100



R^1 = Ph, *p*-$MeOC_6H_4$, 2,4-dimethoxypyrimidin-5-yl
R^2 = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *m*-ClC_6H_4

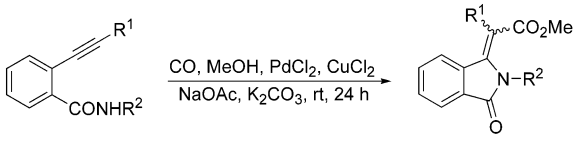
were obtained in good yields except for diphenylacetylene (Scheme 98).

The palladium-catalyzed heteroannulation methodology described by Yum et al. in Scheme 97 was extended to the synthesis of a series of 1,2,3-trisubstituted pyrrolo[3,2-*c*]quinolines from 4-amino-3-iodoquinoline derivatives and internal alkynes (Scheme 99).[141]

A new strategy was reported by Kundu et al. to achieve the regio- and stereoselective synthesis of isoindolinones via palladium-catalyzed coupling of *o*-iodobenzamides with terminal alkynes and subsequent cyclization (Scheme 100).[142] Cyclization occurred under the coupling reaction conditions [Pd-$(PPh_3)_2Cl_2$, CuI, Et_3N, DMF] or from the intermediate 2-alkynylbenzamides by treatment with the Pd-$(OAc)_2$−LiCl−K_2CO_3−DMF system or in basic medium. Reactive alkynes (e.g., phenylacetylene, *m*-chlorophenylacetylene) lowered the yields due to dimerization, whereas *m*-chlorophenyl and *p*-anisyl substitution on the nitrogen of the *o*-iodobenzamides led to a very fast cyclization, with excellent overall yields of the isoindolinones.

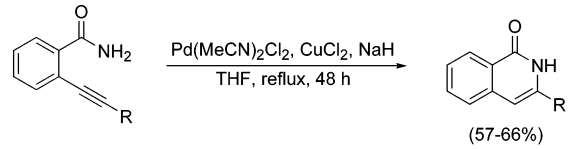
Similar to the above reaction but starting from 2-alkynylbenzamides in the presence of carbon monoxide and methanol under basic conditions, the sequential cyclization−carbonylation gave rise to

Scheme 101



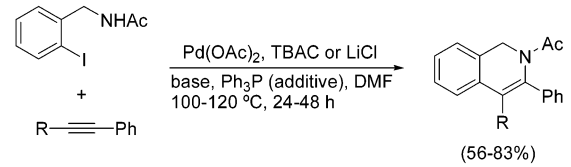
R^1 = Bu^n, Ph
R^2 = H, Me

Scheme 102



R = Pr^n, Bu^n, $Pent^n$, Hex^n, Ar

Scheme 103



R = Me, Ph, CO_2Et, CHO

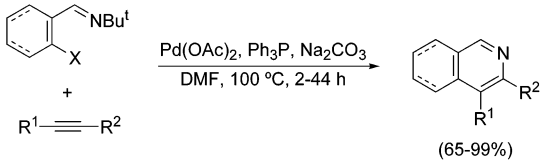
3-alkylideneisoindolinones in low to moderate yields (Scheme 101).[103]

In contrast to the above reaction, opposite regioselectivity was observed when primary 2-alkynylbenzamides were refluxed with $Pd(MeCN)_2Cl_2$, $CuCl_2$, and NaH in THF for 48 h, giving the corresponding isoquinolin-1-ones in 57−66% yield (Scheme 102).[143] The same 6-*endo*-*dig* cyclization mode was observed by Sashida et al. in the cyclization of *N*-butyl-2-ethynylbenzamides catalyzed by $PhCH_2Pd(PPh_3)_2Cl$.[144]

The synthesis of isoquinoline derivatives mediated by palladium was first reported in the late 1980s by Heck et al.[145] However, the reaction was stoichiometric in palladium since it involved the reaction of cyclopalladated *N*-substituted benzaldimine tetrafluoroborates with disubstituted alkynes. The catalytic version for this heterocyclic synthesis would be later introduced by Larock's group.

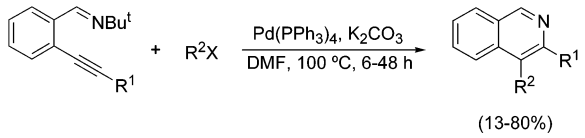
Larock et al. proved that the palladium-catalyzed heteroannulation of internal alkynes is a valuable route to the synthesis of diverse nitrogen-containing heterocycles, such as 1,2-dihydroisoquinolines, isoquinolines, tetrahydroisoquinolines, pyrindines, and pyridines. Thus, starting from 2-(acetamidomethyl)-iodobenzene and internal alkynes containing aryl or carbonyl groups, good yields of the corresponding 1,2-dihydroisoquinolines were obtained (Scheme 103). The process followed the general pattern of regioselectivity already described.[146] The rest of the heterocycles mentioned above were obtained with high regioselectivity starting from *N*-*tert*-butylimino derivatives (acyclic, cyclic, and aromatic) under similar reaction conditions (Scheme 104).[147] Unfortunately, the reaction could not be applied to dialkyl-substituted acetylenes, the presence of an aryl group being essential for the obtention of the heterocycle. A reaction mechanism was proposed in which oxidative addition of the aryl or vinyl halide to Pd(0) took place,

Scheme 104

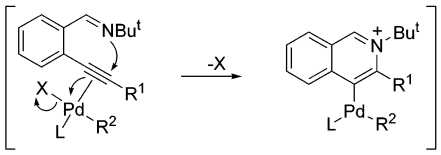


R^1 = Me, Et, Ph, CO_2Et, CH_2OH, CH(Me)OH
R^2 = Ph, PhC≡C, C(Me)CH_2
X = Br, I

Scheme 105



R^1 = alkyl, vinyl, aryl
R^2 = aryl, allyl, benzyl, alkynyl
X = Cl, Br, I



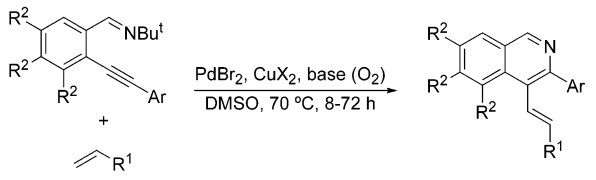
reaction intermediates

followed by alkyne insertion to produce a vinylic palladium intermediate. Reaction of the latter with the neighboring imine group would form a seven-membered palladacyclic ammonium salt, which by subsequent reductive elimination would furnish a *tert*-butylisoquinolinium salt and Pd(0). Apparently, the *tert*-butyl group fragmented in order to relieve the strain resulting from the interaction with the substituent present at the 3-position.

Alternatively, the synthesis of 3,4-disubstituted isoquinolines could be accomplished by introducing the group at the 4-position through the palladium-catalyzed cross-coupling of *N*-*tert*-butyl-*o*-(1-alkynyl)-benzaldimines with aryl, allyl, benzyl, and alkynyl halides (Scheme 105).[148] Aryl iodides bearing an electron-withdrawing group at the *para*- and *meta*-positions afforded 4-aryl-3-phenylisoquinolines in good yields, whereas with aryl iodides substituted at the *ortho*-position the reaction failed, probably due to steric hindrance to coordination of the arylpalladium intermediate to the alkyne triple bond. A reaction mechanism was proposed involving the following steps: (a) oxidative addition of the organic halide to the Pd(0) catalyst, (b) coordination of the resulting palladium intermediate to the alkyne triple bond and consequent activation toward nucleophilic attack, (c) intramolecular nucleophilic attack, (d) reductive elimination with simultaneous regeneration of the Pd(0) species, and (e) cleavage of the *tert*-butyl group from the nitrogen atom with release of the strain between this group and the R^1 group to form the 3,4-disubstituted isoquinoline. Applying the same reaction conditions but using $Bu^n{}_3N$ as base instead of K_2CO_3 under 1 atm of CO, carbonylative cyclization occurred to furnish the corresponding 3-substituted 4-aroylisoquinolines.[149]

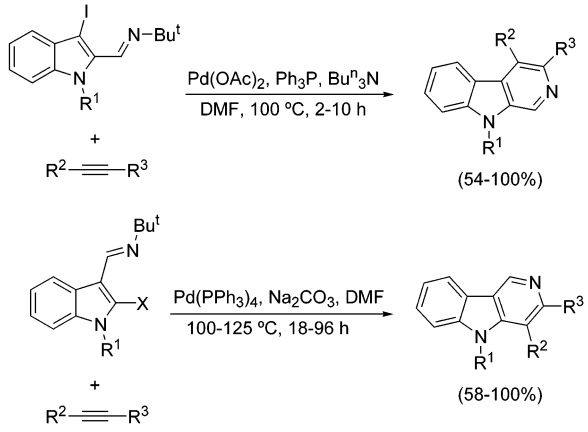
Recently, this methodology has been extended to the synthesis of 4-(1-alkenyl)-3-isoquinolines by palladium(II)-catalyzed cyclization of 2-(1-alkynyl)benzaldimines followed by Heck reaction (Scheme 106).[150] Two different procedures were developed for the above synthesis, involving the systems $PdBr_2$–$Cu(OAc)_2$–NaOAc–DMSO or $PdBr_2$–$CuCl_2$–$NaHCO_3$–DMSO–O_2. Better yields were obtained when an *ortho*-methoxy group was present on the benzaldimine moiety, probably due to fact that it helps directing the $PdBr_2$ to the vicinity of the internal triple bond and stabilizes the resulting Pd(II) intermediate after cyclization. The only inconvenience of this process seems to be the obtention in some cases of the corresponding monosubstituted isoquinolines as byproducts.

Scheme 106



Ar = Ph, *p*-$MeOC_6H_4$, *o*-$MeOC_6H_4$
R^1 = Ph, CMe_2OH, OBu^n, CO_2Bu^n, CO_2Bu^t, SO_2Ph, $CONMe_2$
R^2 = H, OMe

Scheme 107



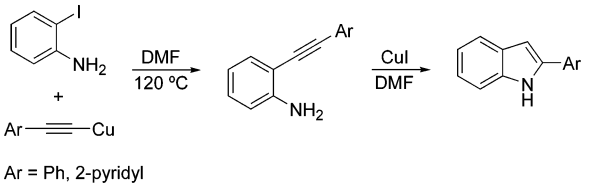
R^1 = H, Me, MOM
R^2 = R^3 = Pr^n, Ph, CH_2OH
R^2 = Ph; R^3 = CO_2Et
X = Br, I

The palladium-catalyzed iminoannulation strategy developed by Larock et al. was extended to the synthesis of a variety of β- and γ-carbolines by the annulation of internal alkynes with the *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-haloindole-3-carboxaldehydes, respectively (Scheme 107).[151] Different reaction conditions had to be used for the obtention of the β- and γ-carbolines, unsymmetrical alkynes leading, in general, to a poor regioselectivity.

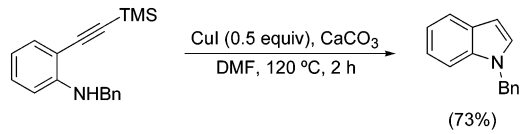
2.3.4. Copper and Other Metals

As early as in the 1960s, Castro et al. already described the high-yielding synthesis of indoles by treating *o*-iodoanilines with cuprous acetylides in refluxing pyridine.[152] It was suggested that both the substitution of the iodide and cyclization took place through a concerted pathway within the same copper complex. It was also discovered that a two-step

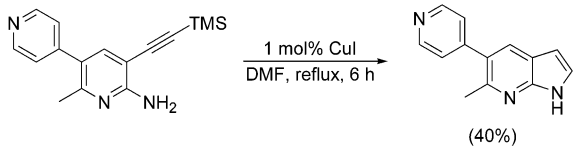
Scheme 108



Scheme 109



Scheme 110



sequence involving coupling of the copper acetylide and smooth cyclization with CuI was preferred, in general, for the preparation of 2-alkylindoles.[153] This could be considered as the first copper(I)-iodide-mediated intramolecular cyclization of 2-alkynylanilines as a useful approach to prepare 2-substituted indoles (Scheme 108).

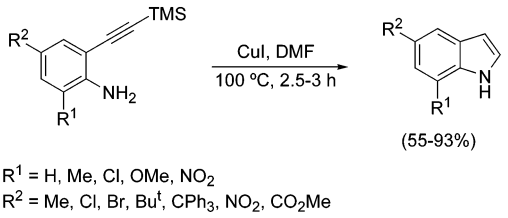
This methodology was utilized by other groups as convenient access to indole synthesis. Thus, Villemin et al. synthesized 2-phenylindole in 99% yield from 2-aminodiphenylacetylene with catalytic CuI (6 mol %) in DMF at reflux for 4 h.[154] Yamamoto et al. also observed that by treatment of *N*-benzyl-2-(trimethylsilylethynyl)aniline with CuI (0.5 equiv) and $CaCO_3$ at 120 °C in DMF, smooth cyclization and concurrent elimination of the TMS group occurred to furnish 1-benzylindole in 73% yield (Scheme 109).[155] Other 2-alkynylanilines, when subjected to the same conditions, produced the corresponding functionalized indoles in excellent yields (84−96%).

Similarly, cyclization of a 3-alkynyl-2-aminopyridine to the corresponding 7-azaindole was accomplished with CuI in refluxing DMF, proteodesilylation also occurring either during the course of the reaction or workup (Scheme 110). However, a 35% yield of the desilylated starting material was obtained as byproduct.[156]

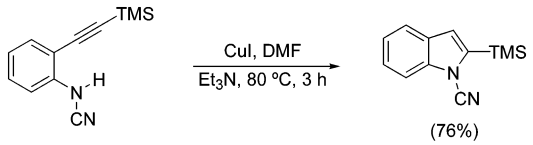
2-(Trimethylsilylethynyl)anilines, prepared by Lamas et al. through the palladium-catalyzed coupling of 2-iodoanilines with (trimethylsilyl)acetylene, were efficiently cyclized under the action of an excess amount of copper(I) iodide with concomitant elimination of the TMS substituent, giving rise to a series of 5-mono- and 5,7-disubstituted indoles in moderate to excellent yields (Scheme 111).[157] Cyclizations were successfully run up to on a 4-g scale, appropriate dialkynyl substrates allowing bisannulation and sequential annulation toward the corresponding benzodipyrroles.

In contrast with the previous examples, the reaction of a silylated (2-alkenylphenyl)cyanamide in the presence of a catalytic amount of CuI (10 mol %) gave

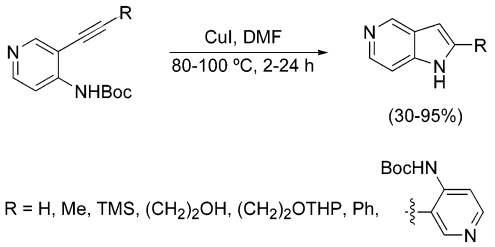
Scheme 111



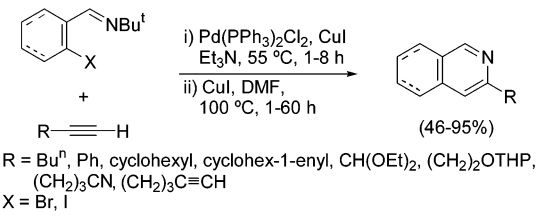
Scheme 112



Scheme 113



Scheme 114

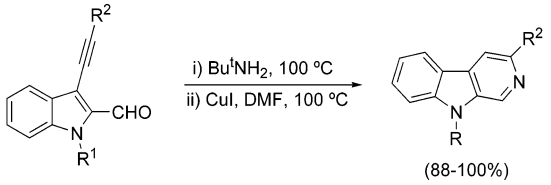


the corresponding indole in 76% yield with no loss of the TMS group (Scheme 112).[158]

This methodology, but using 2 mol % CuI, also found application in the cyclization of 3-alkynyl-4-aminopyridine derivatives to 2-substituted-5-azaindoles, this reaction being quite general for a variety of substituted acetylenes (except for those bearing silyl groups) (Scheme 113).[159] Although yields were relatively low when a free hydroxyl group was present, they were improved by appropriate protection. The alkoxycarbonyl group seemed to be the best accepted activating group on nitrogen for the cyclization reaction, whereas when the nitrogen atom was unsubstituted or had a tosyl or acetyl group, the starting material was recovered unchanged.

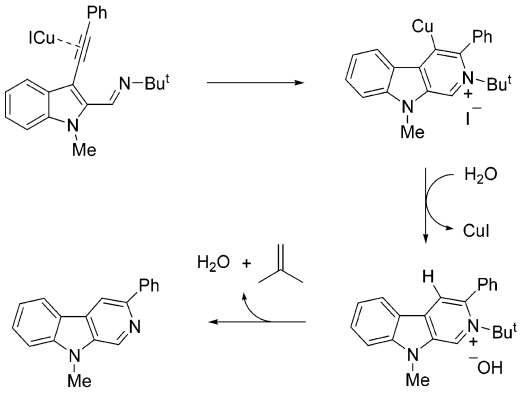
Larock et al. reported the synthesis of monosubstituted isoquinolines, naphthyridines, and pyridines by the coupling of terminal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst and subsequent copper-catalyzed (10 mol %) cyclization of the intermediate iminoalkynes (Scheme 114).[160] The process could be effected in a two-step sequence or in a single step, products being obtained in good to excellent yields. Alternatively, the silver-catalyzed ring closure was also very effective in the cyclization of aryl-, alkenyl-, and alkyl-substituted iminoalkynes under mild reaction conditions (5 mol % $AgNO_3$, $CHCl_3$, 50 °C).[161]

Scheme 115



R^1 = Me, Bn, MOM
R^2 = Ph, Oct^n, Cy, cyclohex-1-enyl, $(CH_2)_2OH$, $(CH_2)_8CO_2Me$, $(CH_2)_3CN$

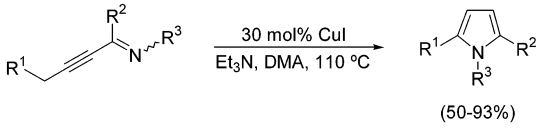
Scheme 116



The palladium-catalyzed synthesis of carbolines described by Larock et al. (see Scheme 107) was complemented by the introduction of changes in the reaction sequence order to favor the final copper-catalyzed annulation. Thus, the palladium−copper-catalyzed Sonogashira coupling of *N*-substituted 3-iodoindole-2-carboxaldehydes with different terminal acetylenes afforded the corresponding 3-alkynyl-1-methylindole-2-carboxaldehydes in very high yields. Conversion of the latter to the corresponding *tert*-butyl imines and subsequent copper-catalyzed cyclization produced the expected 3-substituted β-carbolines in excellent yields (Scheme 115).[162] The methodology was applicable to aryl-, alkenyl-, and alkyl-substituted terminal acetylenes, being compatible with the presence of hydroxy, ester, and cyano functionalities. A reaction mechanism was proposed involving copper(I) coordination to the carbon−carbon triple bond, followed by intramolecular nucleophilic attack of the imine nitrogen atom forming a copper β-carbolinium intermediate (Scheme 116). Apparently, negligible amounts of water present in the system protonated that intermediate, regenerating CuI and producing a carbolinium salt, which relieves strain by fragmentation of the *tert*-butyl group, leading to the β-carboline.

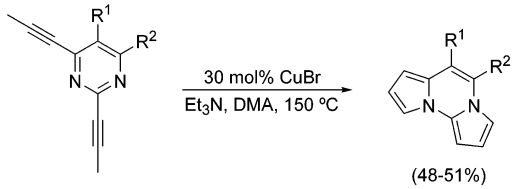
A novel copper-assisted cycloisomerization of acyclic alkynyl imines was recently described by Gevorgyan et al. and applied to the efficient synthesis of pyrroles and pyrrole-containing heterocycles.[163] Most of the experiments were performed with the easily deprotectable 3-(ethyl butyryl) group on the nitrogen atom, the method being compatible with the presence of different functional groups and leading to the corresponding 2-monosubstituted and 2,5-disubstituted pyrroles in moderate to excellent yields (Scheme 117). This approach was extended to starting cyclic alkynyl imines containing pyridine, quinoline, isoquinoline, pyrimidine, and thiazole moieties, thus

Scheme 117



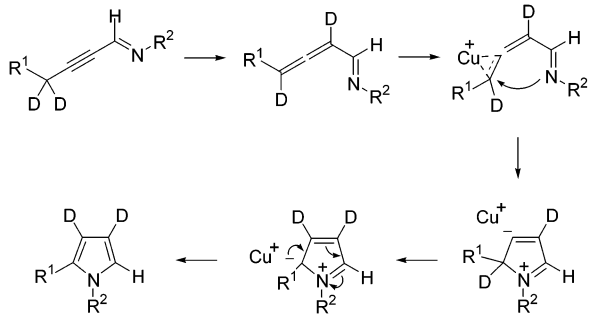
R^1 = H, Pr^n, Bu^n, OTBDMS, CH_2OTBDMS, $(CH_2)_2CN$, $(CH_2)_3CH{=}CH_2$
R^2 = H, Me, Pr^n, Ph
R^3 = Bu^n, Bu^t, Ph, Tr, 3-(ethyl butyryl)

Scheme 118

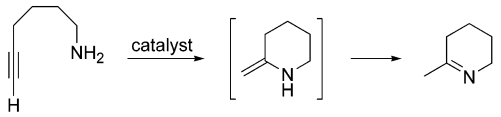


R^1, R^2 = H, Me

Scheme 119



Scheme 120



providing various types of nitrogen-containing heteroaromatic compounds in a straightforward manner. The utility of this methodology was demonstrated in the synthesis of (±)-monomorine. Even more spectacular is the copper-assisted double pyrrolization of a bis-alkynylpyrimidine to afford a 5−6−5 tricyclic heteroaromatic skeleton, used as an immediate precursor for the diastereoselective synthesis of (±)-tetraponerine T6 (Scheme 118).[164] Experimental support is in agreement with a mechanistic proposal including a base-induced propargyl−allenyl isomerization and coordination of copper to the terminal bond of the allene, followed by intramolecular nucleophilic attack. The resulting zwitterion would isomerize into a more stable one, which would lead to the pyrrole system (Scheme 119).

Müller et al. reported a very detailed comparative study on the catalytic activity of various early-transition-metal catalysts for the cyclization of 6-aminohex-1-yne to 2-methyl-1,2-dehydropiperidine (Scheme 120).[59] The highest catalytic activity was observed for the copper(I) compound $[Cu(MeCN)_4]$-PF_6, close to quantitative conversions also being reported for group 12 metal salts such as $Zn(CF_3SO_3)_2$, $Cd(NO_3)_2{\cdot}4H_2O$, and $Hg(NO_3)_2$. Moderate conversions were achieved with $AgBF_4$ and $AuCl_3$ despite partial metal salt decomposition, the addition of

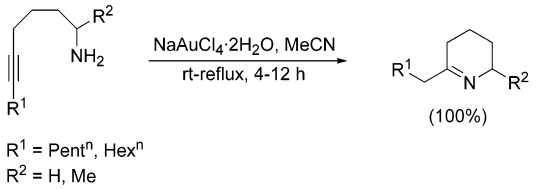
phosphines to increase their stability dropping, on the other hand, their catalytic activity. Low catalytic activity was observed for the cobalt and nickel complexes $K[Co(CO)_3(PPh_3)]$ and $Ni(PPh_3)_4$.

This work was further extended to the catalytic cyclization of aminoalkynes of general formula $RC{\equiv}C(CH_2)_nNH_2$ (R = H, Ph, n = 3; R = H, n = 4) and 2-(phenylethynyl)aniline.[77] $[Cu(MeCN)_4]PF_6$ and $Zn(CF_3SO_3)_2$ exhibited catalytic activities comparable to those based on organolanthanides, whereas 37% conversion was observed with $[Re(CO)_6(H_2O)]BF_4$ after 20 h in toluene under reflux. It was demonstrated that the Lewis acidity of the metal is crucial for its catalytic activity, since the reaction pathway involves coordination of the carbon−carbon triple bond to the metal. Kinetic studies with $[Cu(MeCN)_4]PF_6$ revealed a first-order dependence of the catalytic rate on substrate and catalyst concentration, consistent with the nucleophilic attack of a coordinated alkyne by the amine, followed by rate-determining protonation of the intermediate β-aminoethenyl complex at the carbon atom attached to the metal. A mechanism similar to that depicted in Scheme 54 was proposed to explain the cyclization of aminoalkynes with groups 7−12 transition-metal catalysts. The effect of the anions on the cyclization of 6-aminohex-1-yne was studied with other metal catalysts such as Ag(I), Hg(II), Cd(II), and Zn(II) salts. Thus, the presence of basic anions, such as $CH_3CO_2^-$, $PhCO_2^-$, and CO_3^{2-}, inhibited the catalytic activity, whereas the highest activities were observed for large anions of low nucleophilicity such as TsO^- and TfO^-. Regarding the effect of water on this cyclization reaction, the catalytic activity of $Zn(TfO)_2$ was not significantly influenced by the addition of up to 4 equiv of H_2O.

The intermolecular hydroamination of 6-aminohex-1-yne to 2-methyl-1,2-dehydropiperidine was also effectively catalyzed by Zn^{2+} ion-exchanged zeolites BEA.[165] These heterogeneous catalysts exhibited superior activity when compared to catalysts based on homogeneous zinc complexes such as $Zn(TfO)_2$, which was attributed to the simultaneous presence of Brønsted and Lewis acid sites in Zn−BEA. A correlation of the Lewis acidity with the catalytic activity was observed for different zinc catalysts, following the trend Zn−BEA > ZnO/SiO_2 > ZnO. A reaction pathway similar to that shown in Scheme 54 was invoked in which the reacting 6-aminohex-1-yne coordinates via its acetylenic bond onto the Zn^{2+} at ion-exchange sites of Zn−BEA. Subsequent amine attack to the coordinated acetylenic bond would result in the formation of a zwitterion, which rearranges to give an intermediate 2-methylidenepiperidine, the latter isomerizing to the final product 2-methyl-1,2-dehydropiperidine.

The remarkable activity of Zn−BEA led the authors to discover the cocatalytic effect observed in the above transformation upon addition of acid (CF_3SO_3H) for different catalysts based on late transition metals.[166] This effect was rationalized in terms of (a) higher probability of coordination of the alkyne moiety to the metal center (since the competitive coordinating amino group would be protonated as the ammonium salt), (b) protolytic cleavage of the metal−carbon bond in the intermediate 2-ammonio alkenyl complex is facilitated under acidic conditions, and (c) isomerization of the enamine to the imine is accelerated in the presence of protons.

Scheme 121



Intramolecular hydroaminations were also efficiently catalyzed in a liquid−liquid two-phase system comprising a polar catalyst phase of $Zn(TfO)_2$ in the ionic liquid 1-ethyl-3-methylimidazolium trifluoromethanesulfonate and a substrate mixture in heptane.[167] The reactions were performed in the batch mode and the mixtures stirred sufficiently fast to obtain a homogeneous suspension of the two phases. Under these reaction conditions, a quantitative conversion of 6-aminohex-1-yne was achieved within 150 min, the reaction rate being higher than the corresponding homogeneous catalysis using $Zn(TfO)_2$ and slightly lower compared to the heterogeneous (solid−liquid) catalysis using Zn−H-beta zeolite as catalyst. The reaction was proposed to take place either in the polar phase or at the phase boundary, involving a polar transition state stabilized in the presence of 1-ethyl-3-methylimidazolium trifluoromethanesulfonate. Unfortunately the intermolecular reaction between phenylacetylene and aniline to give phenyl-(1-phenylethylidene)amine proceeded slowly (10% conversion after 150 min).

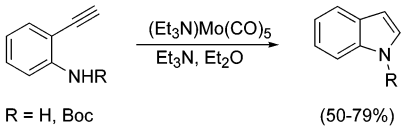
Au(III) was also found to be effective in the formation of 2,6-dialkyl- and 6-alkyl-2,3,4,5-tetrahydropyridines from the corresponding 5-alkynylamines (Scheme 121).[168] The reactions were performed under mild and neutral conditions, providing quantitative yields of the tetrahydropyridines. The results obtained under the action of $NaAuCl_4{\cdot}2H_2O$ as catalyst were better in comparison with those obtained with $Pd(MeCN)_2Cl_2$.

The cyclization of 2-alkynylanilines to the corresponding indoles, via intermediate 3-indolylpalladium species, reported by Utimoto et al. and previously mentioned (see Scheme 71), was also successfully achieved using $NaAuCl_4{\cdot}2H_2O$ as catalyst.[100] Unfortunately, trapping of the assumed intermediary 3-indolylaurate with allyl chlorides failed to give mainly the 2-alkylindoles and small amounts of the alkylated products.

It has been shown that $Ni(CO_2)_2(PPh_3)_2$ in refluxing EtOH can also promote the intermolecular hydroamination of 6-aminohex-1-yne to give 2-methyl-3,4,5,6-tetrahydropyridine hydrochloride in 60% yield.[169] $Ni(CO)_2(PPh_3)_2$ was a moderately effective catalyst in the reaction with alkynylamines of the type $ArC{\equiv}C(CH_2)_nNH_2$ (Ar = Ph, p-MeC_6H_4; n = 2, 3), furnishing the corresponding 3,4-dihydro-2*H*-pyrroles in 40−67% yield.[62]

Finally, McDonald et al. described the group VI metal-promoted intramolecular hydroamination of

Scheme 122



alkynylamines.[170] *N*-Boc-protected acyclic aminoalkynes were cyclized in the presence of stoichiometric amounts or excess amounts (1−5 equiv) of (Et_3N)-$Mo(CO)_5$, $(THF)W(CO)_5$, and $Cr(CO)_6$, the reaction proceeding via the corresponding vinylidene carbenes. On the other hand, only the cyclization of 2-alkynylanilines could be accomplished with catalytic amounts of the metal carbonyl reagent, giving the corresponding indoles in moderate to good yields (Scheme 122).

3. Hydroalkoxylation

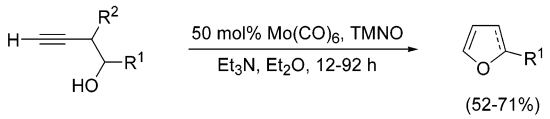
The addition of alcohols to alkynes can be considered a direct way toward the synthesis of enol ethers and a wide variety of oxygen-containing heterocycles, according to the inter- or intramolecular mode of reaction, respectively. Despite the different studies carried out on the nucleophilic addition of alcohols to alkynes in superbasic catalytic systems, namely, alkali-metal hydroxides,[6,171] transition-metal compounds are still the catalysts of choice to carry out the hydroalkoxylation of alkynes due to their effectiveness and wide scope of application.[172] Again, palladium catalysts dominate by far in this field through reaction mechanisms similar to those described for hydroamination processes.[69a−c,g,95e,173,174] On the other hand, metal vinylidene intermediates derived from terminal alkynes and metals such as chromium, molybdenum, tungsten, and ruthenium have also found application in these reactions, formerly used in stoichiometric amounts and more recently adapted to some catalytic systems.[61,175]

3.1. Molybdenum, Tungsten, and Ruthenium Catalysts

The cycloisomerization of alkynyl alcohols to endocyclic enol ethers through metal vinylidenes was first introduced by McDonald.[175] This group has practically developed all the chemistry on this field involving complexes of the middle and late transition metals in a stoichiometric up to a catalytic fashion. We will only mention those examples in which the reactions proceed under substoichiometric or catalytic amounts of those complexes.

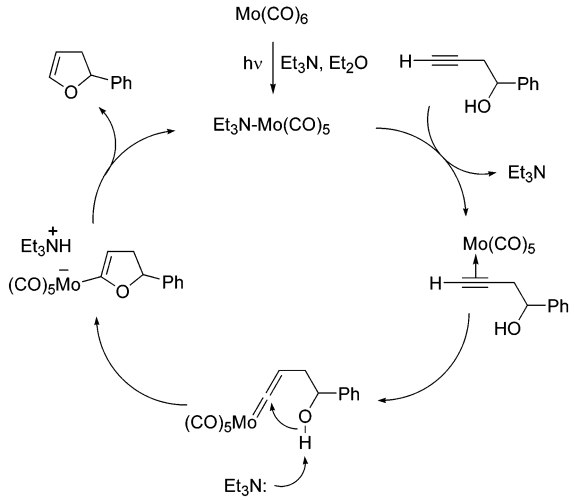
For instance, in one of the first accounts, McDonald et al. reported a new synthesis of 2,3-dihydrofurans based on the cycloisomerization of 3-alkyn-1-ols with molybdenum hexacarbonyl and trimethylamine *N*-oxide (TMNO).[176] The best preparative yield and reproducibility were observed with 50 mol % $Mo(CO)_6$ and TMNO, triethylamine as cosolvent accelerating the reaction rate (Scheme 123). Substrates bearing a heteroatom substituent at the 2-position of the alkynol underwent elimination to give the corresponding furan derivatives. Although the generation of $Mo(CO)_5$ from $Mo(CO)_6$ and TMNO produced a modestly catalytic reagent, the authors found that $Et_3N-Mo(CO)_5$ was better prepared by photolysis of

Scheme 123

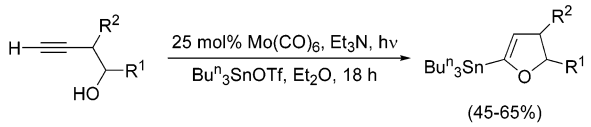


R^1 = Ph, CH_2OH, CH_2OPiv, $CH_2OTBDMS$
R^2 = H, OH, N_3

Scheme 124



Scheme 125



R^1 = H, Ph
R^2 = H, Me

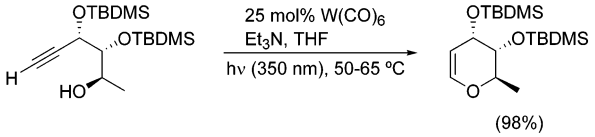
$Mo(CO)_6$ in a mixture of diethyl ether and triethylamine.

The reaction was suggested to proceed by initial rearrangement of a η^2-metal−alkyne complex to a vinylidene complex, followed by base-induced cyclization giving a cyclic anionic intermediate. Protonation at C1 would afford the dihydrofuran product with regeneration of $Et_3N-Mo(CO)_5$ as a potential catalyst (Scheme 124).[177] This transformation of alkynyl alcohols into endocyclic enol ethers was used as the key step in the asymmetric synthesis of stavudine and cordycepin,[178] both deoxynucleosides exhibiting high antiviral and antibiotic activities, respectively, as well as in the asymmetric synthesis of many other nucleosides.[179]

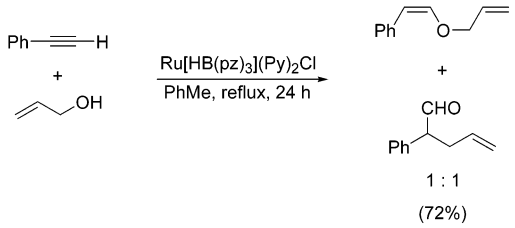
The catalytic molybdenum carbene anion intermediate generated in the above alkynol cyclization could be trapped with tri-*n*-butyltin triflate, furnishing several α-(tri-*n*-butylstannyl)dihydrofurans in moderate yields but in a very practical manner (Scheme 125).[180]

Initial work to extend the alkynol cycloisomerization methodology to the synthesis of the homologous 3,4-dihydro-2*H*-pyrans required the use of stoichiometric amounts or excess tungsten hexacarbonyl, the reaction taking place in two steps through the corresponding cyclic six-membered tungsten oxacarbenes.[181] More recently, the single-step cycloisomer-

Scheme 126



Scheme 127



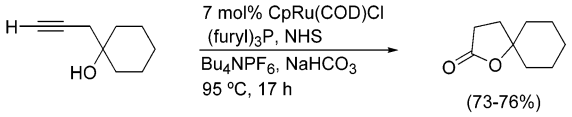
ization of 1-alkyn-5-ols with catalytic amounts of $W(CO)_6$ under 350 nm photolysis at or near THF reflux in the presence of triethylamine was achieved.[182] A wide variety of diastereomeric 6-deoxy-1,2-glycals were prepared in very good yields through the corresponding tungsten vinylidene catalytic intermediates (Scheme 126). Although the reaction must be carried out under strict anaerobic conditions, the high yields obtained and lower catalyst loading represent a significant improvement with respect to the previously reported protocols.

A mechanism similar to the one depicted in Scheme 124 was proposed to account for the obtention of the 3,4-dihydro-2*H*-pyran moiety, being supported by computational studies carried out with 4-pentyn-1-ol as a model compound.[183] Very high activation barriers of 50−55 kcal/mol were obtained for both the *endo*- and *exo*-cycloisomerizations in the absence of catalyst. With the tungsten pentacarbonyl catalyst the *endo*-cycloisomerization was found to proceed with a rate-determining barrier of 26 kcal/mol at the hydride migration step to form a vinylidene intermediate. Thus, the most important role of the catalyst seems to be the stabilization conferred to the vinylidene structure by forming a strong vinylidene−tungsten bond.

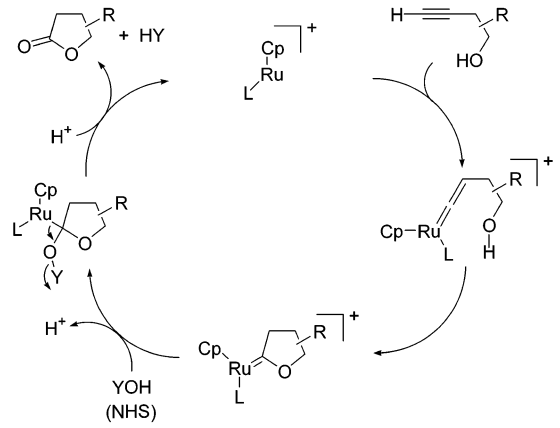
The utility of this methodology was demonstrated in the stereoselective synthesis of disaccharide substructures of the landomycin and mithramycin families of anticancer antibiotics,[184] the convergent synthesis of digitoxin,[185] the stereoselective synthesis of vancosamine and saccharosamine glycals,[186] and the synthesis of L-oliose trisaccharide.[187]

The electrophilic activation of terminal alkynes by suitable ruthenium(II) catalysts also promotes both inter- and intramolecular hydroalkoxylation processes.[61a] The first intermolecular addition of allyl alcohols to acetylenes under ruthenium catalysis seems to be that reported by Kirchner et al. in the mid 1990s.[188] Thus, by heating phenylacetylene and an excess amount of allyl alcohol with 2 mol % of new ruthenium complexes of the tris(pyrazolyl)borate ligand $[HB(pz)_3]$,[189] a 1:1 mixture of the *cis*-allyl vinyl ether and the aldehyde derived from the Claisen rearrangement of the *trans*-allyl vinyl ether was obtained (Scheme 127). A vinylidene complex was proposed as the likely reactive intermediate in this catalytic process.

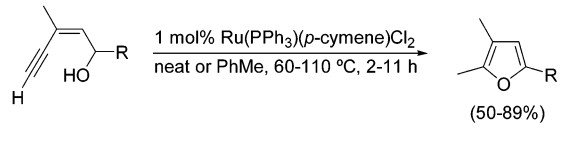
Scheme 128



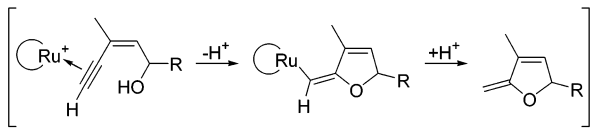
Scheme 129



Scheme 130



R = H, Et, Ph, *o*-$CH_2C_5H_4N$, $CH_2CH{=}CH_2$, CN, C≡CPh, C≡CTMS



suggested reaction intermediates

Trost et al. developed a ruthenium-catalyzed cycloisomerization−oxidation of homopropargyl alcohols that converts them into the corresponding γ-butyrolactones (see an example in Scheme 128).[190] The reaction was performed with CpRu(COD)Cl and tri(furyl)phosphine as precatalyst, in the presence of tetra-*n*-butylammonium bromide or hexafluorophosphate, sodium bicarbonate, and *N*-hydroxysuccinimide (NHS) as the oxidant, in DMF−H_2O at 95 °C. A catalytic cycle was proposed involving the corresponding vinylidenemetal species and metal-complexed oxacarbenes (Scheme 129). A wide variety of γ-butyrolactones were synthesized by this method, most of them being natural products with important biological activities.

Dixneuf et al. described a very interesting synthesis of furans by selective cyclization of (*Z*)-pent-2-en-4-yn-1-ols in the presence of $Ru(PPh_3)(p\text{-cymene})Cl_2$ as catalyst precursor (Scheme 130).[191] Although the reaction was specific for terminal alkynes, participation of a vinylidene−ruthenium intermediate was ruled out since that pathway would lead to a six-membered cyclic product not detected by the authors. Instead, a mechanism based on the electrophilic activation of the carbon−carbon triple bond followed by intramolecular addition of the hydroxy group to the internal alkyne carbon atom was suggested.

3.2. Palladium and Platinum Catalysts

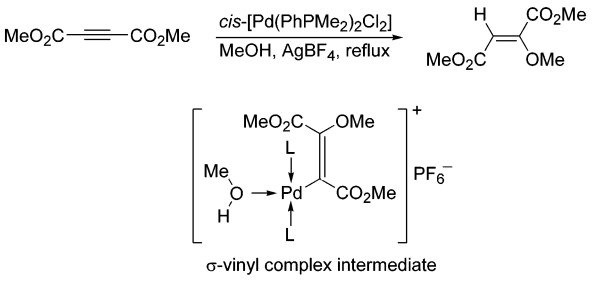
As in hydroamination processes, palladium catalysts are again the most used in the addition of alcohols to alkynes.[173,192] We will deal first with the less studied intermolecular reactions (including also some platinum catalysts), though it will be the intramolecular version that will occupy the main body of this section with special mention of the synthesis of benzofurans.

3.2.1. Intermolecular Additions

In general, the intermolecular addition of alcohols to alkynes is more difficult to accomplish than the intramolecular process, thus requiring stronger Lewis acidic catalysts. In the early 1970s, Clark et al. reported the activation of alkynes toward the intermolecular addition of alcohols with platinum(II) complexes. Thus, *trans*-$PtClMe(PhPMe_2)_2$ and *trans*-$PtClMe(Me_3As)_2$ reacted with electron-deficient acetylenes (RC≡CR, R = CO_2H, CO_2Me) and $AgPF_6$ in MeOH to give the methyl vinyl ether complexes *trans*-$PtCl[RC{=}CR(OMe)](PhPMe_2)_2$ and *trans*-$PtCl[RC{=}CR(OMe)](Me_3As)_2$, respectively.[193] The same result was obtained by Walker et al. but starting from $Pt(dppe)Cl_2$.[194]

Apparently, the first catalytic version of this reaction was carried out by Parkins et al. This group discovered that *cis*-$[Pd(PhPMe_2)_2Cl_2]$ catalyzed the addition of methanol to dimethyl acetylenedicarboxylate (DMAD) in the presence of $AgBF_4$ under reflux to give dimethyl methoxymaleate (Scheme 131).[195]

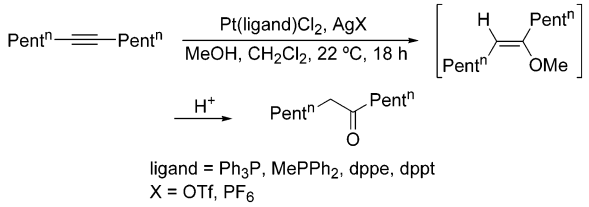
Scheme 131



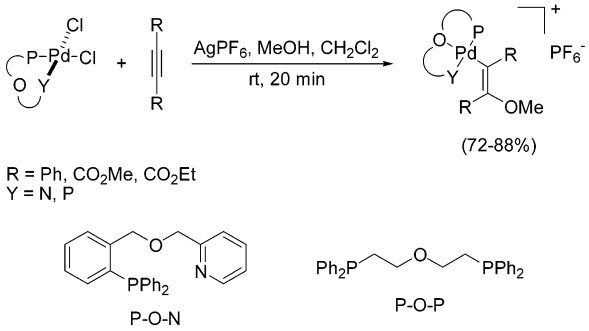
The reaction performed with the homologous platinum complex was much slower, probably due to the higher stability of the Pt−C bond in the σ-vinylplatinum complex. Concerning the reaction stereochemistry, the *trans*-addition mode suggested a MeOH attack from outside the coordination sphere, the resulting vinyl complex suffering protonolysis in the acidic reaction medium.

Further research on the above reaction was undertaken by Tani et al. with dicationic catalysts derived from $Pt(ligand)Cl_2$ and $Pd(ligand)Cl_2$, different phosphines having been tested as ligands. In contrast to the results reported by Parkins et al., this group observed that, in general, the dicationic platinum catalysts were more active toward the addition reaction than the corresponding palladium catalysts, bidentate diphosphine ligands (dppe and dppt) showing better behavior than monophosphine ligands or the potentially tridentate ligand $Ph_2P(CH_2)_2O(CH_2)_2PPh_2$.[196] Moreover, several dicationic platinum complexes derived from $Pt(ligand)Cl_2$ and a silver salt could be applied to the catalytic addition of methanol to nonactivated alkynes, yielding after hydrolysis the corresponding ketones (Scheme 132).[197] The catalytic activity was influenced by the phosphine ligand, silver counterion, and the ratio of the dichloroplatinum complex to the silver salt. Under these reaction conditions, the addition of MeOH to unsymmetrical alkynes produced different ratios of the two regioisomeric ketones, the regioselectivity being influenced by both electronic and steric effects.

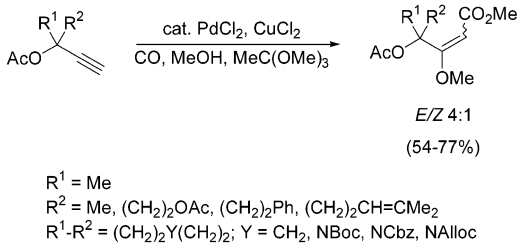
Scheme 132



Scheme 133



Scheme 134

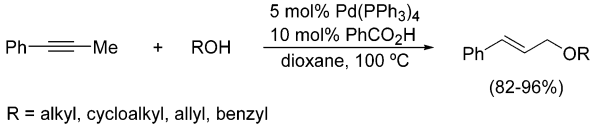


Some insight into the reaction pathway of these processes was brought out by the preparation and characterization of a series of (*E*)-σ-alkenylpalladium complexes having P−O−N or P−O−P tridentate ligands as stabilized intermediates in the palladium-catalyzed stereoselective addition of methanol to activated acetylenes (Scheme 133).[198]

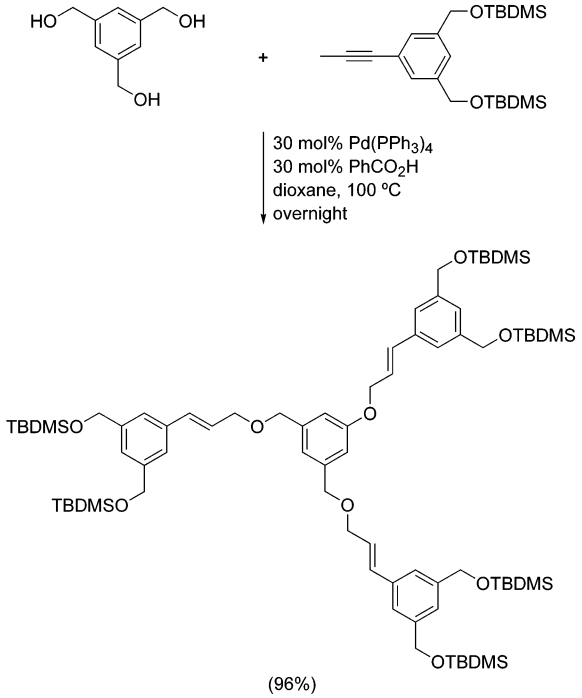
Okumoto et al. described a new carbonylative transformation of propargylic acetates into 4-acetoxy-3-methoxy-2-alkenoate derivatives with MeOH and CO in the presence of a catalytic amount of $PdCl_2$, a stoichiometric amount of $CuCl_2$, and $MeC(OMe)_3$ as a HCl scavenger (Scheme 134).[199] The presence of the acetoxy group was found indispensable to achieve moderate to good yields.

The study carried out by Yamamoto et al. concerning the palladium−benzoic-acid-catalyzed intermolecular addition of secondary amines to internal alkynes[70] was extended to the hydroalkoxylation of 1-phenylprop-1-yne, giving rise to a variety of allylic ethers in good to excellent yields (Scheme 135).[200] A

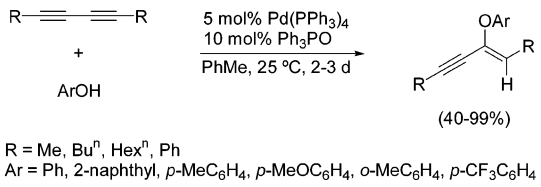
Scheme 135



Scheme 136



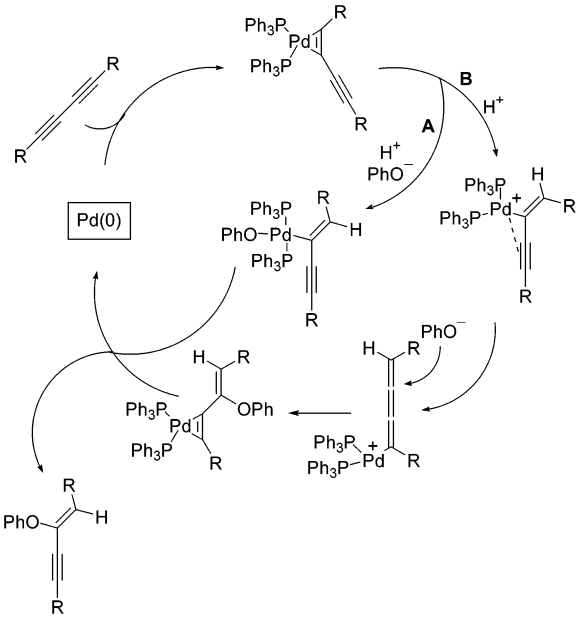
Scheme 137



mechanism similar to that proposed for the previously described hydroamination process was suggested (see Scheme 48). As a very interesting application of this methodology, the authors optimized the synthesis of a first-generation dendrimer by premixing the catalytic system followed by the addition of a triol and a conveniently substituted alkyne (Scheme 136). Identical protocol was followed by Zhang et al. to prepare a variety of allylic ethers in good yields (66−89%) from 1-phenylprop-1-yne and primary, secondary, and tertiary alcohols.[201]

Yamamoto's group also described the regio- and stereoselective addition of different phenols and 2,2,2-trifluoroethanol to conjugated diynes catalyzed by palladium(0) in an unusual anti-Wacker-type process.[202] Single addition of the phenol to one of the triple bonds occurred, the presence of additional ligands such as Ph_3PO increasing the reaction yields. Reactions proceeded under very mild conditions, though relatively long reaction times were required, the exclusive *trans*-addition furnishing the corresponding (*Z*)-phenoxyenynes in good to high yields (Scheme 137). The fact that no reaction took place with palladium(II) catalysts or with nonacidic aliphatic alcohols and the good behavior of the electron-rich Pd(0) utilized suggested a mechanism involving addition of an electrophilic species (such as a proton) to the diyne system. A plausible reaction pathway could involve the coordination of the Pd(0) species to one of the triple bonds, giving an electron-rich η^2-coordinated Pd(0) complex followed by regioselective addition of a proton (forming a palladium phenoxide) and subsequent reductive elimination (route A) (Scheme 138). Alternatively, addition of a proton to the η^2-coordinated Pd(0) complex followed by rearrangement would lead to a σ-cumulenylpalladium complex. Phenoxide attack to the latter (opposite to the bulky phosphine ligands) and reductive elimination would provide the product with Pd(0) regeneration (route B).

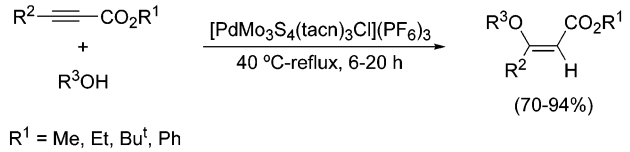
Scheme 138



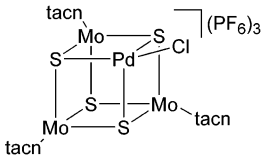
Hidai et al. observed that polynuclear transition-metal−sulfur complexes exhibited a remarkable catalytic activity for the highly regio- and stereoselective addition of alcohols to certain alkynes.[203] Thus, the single-cubane-type cluster $[PdMo_3S_4(tacn)_3Cl](PF_6)_3$ (tacn = 1,4,7-triazacyclononane) was found to catalyze the reaction of a series of alkynic acid esters with alcohols (MeOH, EtOH, BnOH), to give the corresponding products resulting from a *trans*-addition (Scheme 139).[204] The terminal propiolic acid esters reacted faster that the internal derivatives, which required longer reaction times for completion, much lower yields of the products being obtained with other palladium compounds such as $Pd(PhCN)_2Cl_2$, Na_2PdCl_4, $Pd(OAc)_2$, $Pd(dba)_2$, or $Pd(PPh_3)_2Cl_2$. The reaction was presumed to proceed at the unique palladium site in the $PdMo_3S_4$ core with retention of the cubane-type core structure, involving (a) coordination of the alkynic acid ester to the Pd site in the cluster, (b) nucleophilic attack of the alcohol to the electron-deficient carbon atom from the outer coordination sphere, and (c) protonolysis of the Pd−C bond to afford the *trans*-addition product (Scheme 140).

The triangular heterobimetallic sulfido cluster $(Cp^*Ir)_2(\mu_3\text{-}S)_2PdCl_2$ also catalyzed the regioselective

Scheme 139

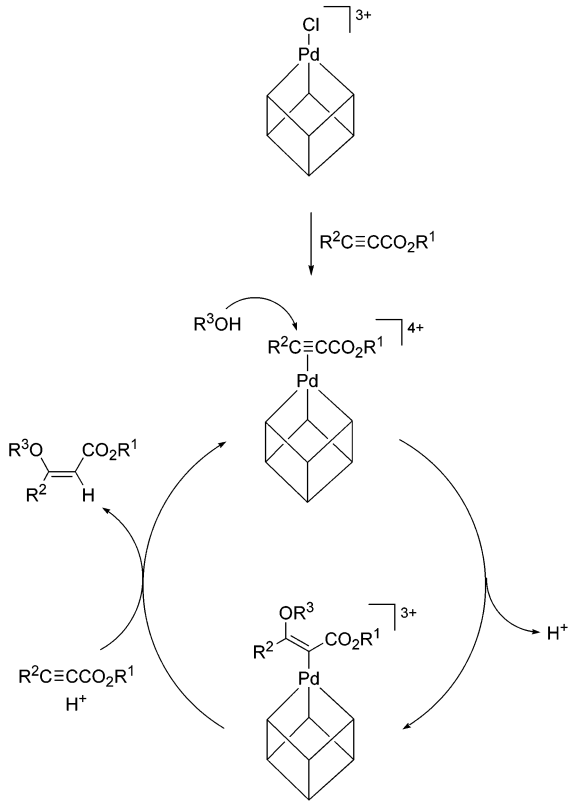


R^1 = Me, Et, Bu^t, Ph
R^2 = H, Me, Ph, CO_2Me
R^3 = Me, Et, Bn

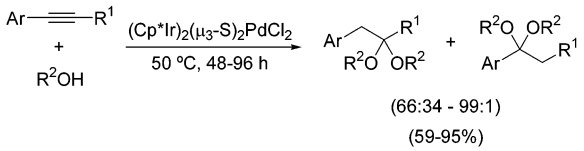


$[PdMo_3S_4(tacn)_3Cl](PF_6)_3$

Scheme 140



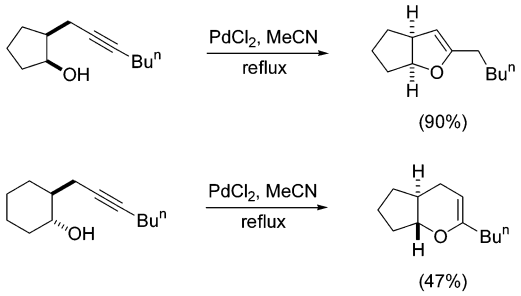
Scheme 141



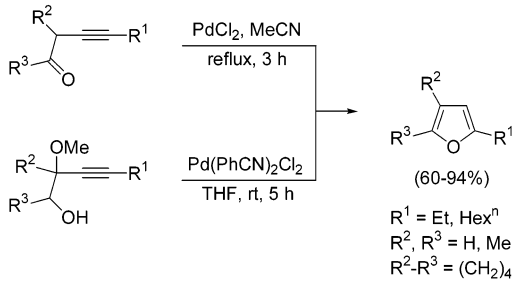
Ar = Ph, *p*-ClC_6H_4, *m*-ClC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$
R^1 = Me, Et, Bu^n
R^2 = Me, Et

addition of alcohols to 1-arylalk-1-ynes, giving in this case the corresponding ketals (Scheme 141).[205] Internal 1-phenyl- and 1-chlorophenylalk-1-ynes showed the highest regioselectivity, whereas 1-arylprop-1-ynes with an electron-donating substituent on the aryl ring showed lower regioselectivity. Opposite regioselectivity was observed for the terminal alkynes PhC≡CH and Hex^{n}C≡CH. Neither monometallic palladium complexes (even with thiolato or thioether ligands), monometallic iridium complexes, nor the combination of $(Cp^*IrCl_2)_2$ and $Pd(COD)Cl_2$ showed any catalytic activity. In close similarity to the above-mentioned example, the authors suggested the formation of an alkoxyvinyl cluster that undergoes nucleophilic attack of the alcohol on the coordinated alkyne molecule at the palladium center of the cluster core.

Scheme 142



Scheme 143



R^1 = Et, Hex^n
R^2, R^3 = H, Me
R^2-R^3 = $(CH_2)_4$

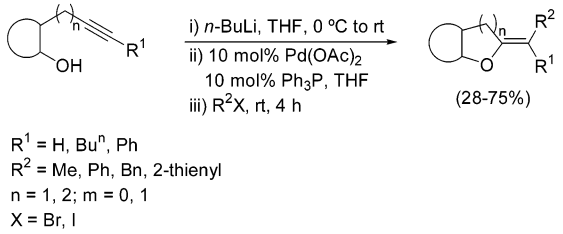
3.2.2. Intramolecular Additions

The intramolecular hydroalkoxylation reaction of hydroxyalkynes has been more deeply studied than the intermolecular version. The importance of this reaction resides in the fact that it provides straightforward methodologies for the construction of very interesting oxygen-containing heterocycles such as furan, pyran, and benzofuran derivatives among others.[69g]

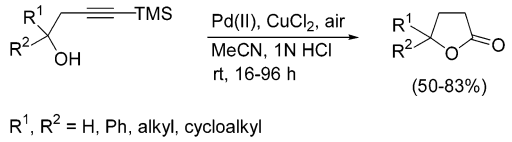
The seminal publication by Utimoto et al. on the palladium-catalyzed synthesis of heterocycles also covers the intramolecular hydroalkoxylation of diverse substrates, promoted by $PdCl_2$ in refluxing MeCN, to furnish the corresponding oxygen-containing heterocycles.[73b] Under these reaction conditions, a bicyclic 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran were prepared from the corresponding alkynols, the size of the ring in the product depending on the relative stereochemistry in the starting alkynol (Scheme 142). However, 3-, 4-, and 5-alkyn-1-ols led to mixtures of the expected dihydrofurans and dihydropyrans together with the ketones resulting from the hydration of the carbon−carbon triple bond. A similar procedure when applied to *β*,*γ*-acetylenic ketones or 2-methoxy-3-alkyn-1-ols afforded the corresponding furans in good to excellent yields (Scheme 143). The power of this methodology was elegantly demonstrated in the synthesis of a series of spiroacetals as well as the pheromones *exo*-brevicomin and frontalin from structurally adequate alkynediols.

The above reactions were proposed to take place through a mechanism similar to that shown in

Scheme 144



Scheme 145



Scheme 51. When the intermediate 3-furylpalladium species derived from either the 2-methoxy-3-alkyn-1-ols or β,γ-acetylenic ketones were trapped with allyl halides, in the presence of an epoxide as a proton scavenger, the corresponding 3-allylfurans were obtained in good to excellent yields.[206]

The previously described work by Luo et al. on the tandem intramolecular aminopalladation of acetylenic amines, followed by the cross-coupling reaction with organic halides (see Scheme 52),[75] was also extended to the oxygenated version. Thus, the successive intramolecular oxypalladation of a wide range of acetylenic alkoxides and cross-coupling with an organic halide gave stereodefined 2-alkylidenetetrahydrofurans and pyrans under very mild reaction conditions (Scheme 144).[207]

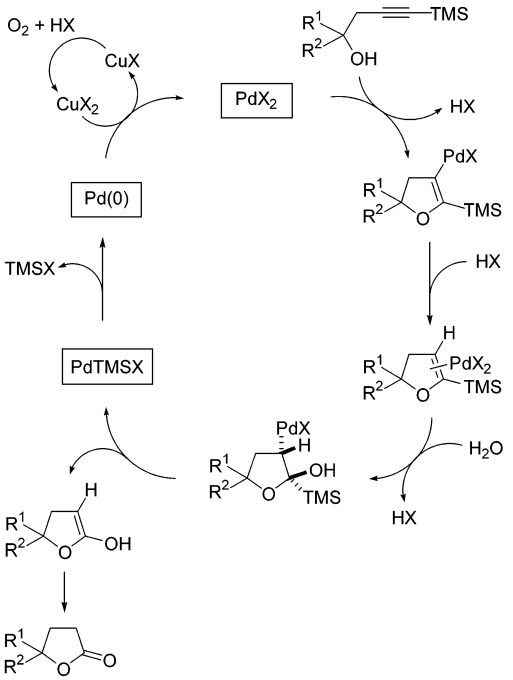
Vatèle et al. discovered a Wacker-related method for the preparation of differently substituted γ-lactones based on the intramolecular hydroalkoxylation of trimethylsilyl homopropargylic alcohols.[208] The best results were obtained when the starting 4-trimethylsilyl-3-alkyn-1-ols were treated with 5% Pd(MeCN)$_2$ClNO$_2$ or Pd(OAc)$_2$ in the presence of 25% $CuCl_2$ in a slightly acidic medium and under an air atmosphere (Scheme 145). The reaction proceeded with complete retention of the configuration for starting diastereo- or enantioenriched alcohols, the presence of the TMS group always being essential for the lactonization to succeed. Experimental support evidenced a plausible catalytic cycle involving a η^2-olefin complex that undergoes hydroxypalladation and subsequent PdX−TMS *syn*-elimination (Scheme 146).

Starting from the homologous ω-silyl-substituted γ-alkynols and in the presence of catalytic amounts of Pd(OAc)$_2$ and hydrochloric acid, exclusive 5-*exo-dig* ring closure took place to give the corresponding 2,3-dihydrofurans with complete loss of the terminal silyl group (Scheme 147).[209] Alkyne hydration was observed as a side reaction, whereas incorporation of $CuCl_2$ to the reaction mixture directly provided the corresponding furans by in situ oxidation.

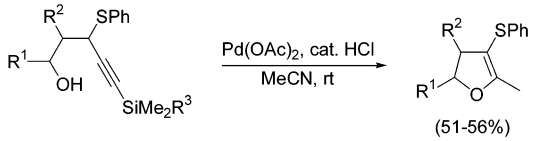
A general route to the synthesis of 2,3,5-trisubstituted furans was reported by Cacchi et al., based on the palladium-catalyzed cyclization of 2-propargyl-1,3-dicarbonyl compounds with vinyl and aryl triflates or halides, in the presence of potassium carbonate (Scheme 148).[210] From a mechanistic point of view, the formation of a π-palladium complex was suggested followed by regioselective *trans*-alkoxypalladation, reductive elimination, and isomerization (Scheme 149). This methodology, applied at higher temperature, was extended to alkyl 3-oxo-6-heptynoates and 3-oxo-7-substituted-6-heptynoates, readily giving new access to 2,5-disubstituted furans (Scheme 150).[211] In this case, aryl halides bearing electron-withdrawing substituents were more efficient than those bearing electron-donating substituents. When the reaction shown in Scheme 148 (R^1 = Me, R^2 = Ar, X = I) was performed under a CO atmosphere, the corresponding 2,3,5-trisubstituted furans bearing two acyl moieties were obtained in moderate yields.[212]

Different cyclic alkenyl ethers were recently synthesized by Yamamoto et al. by reacting alkynyl aldehydes with methanol under Pd(II) catalysis.[213] The reaction was carried out with catalytic Pd(OAc)$_2$

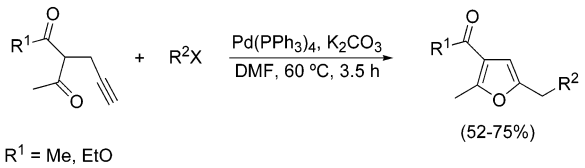
Scheme 146



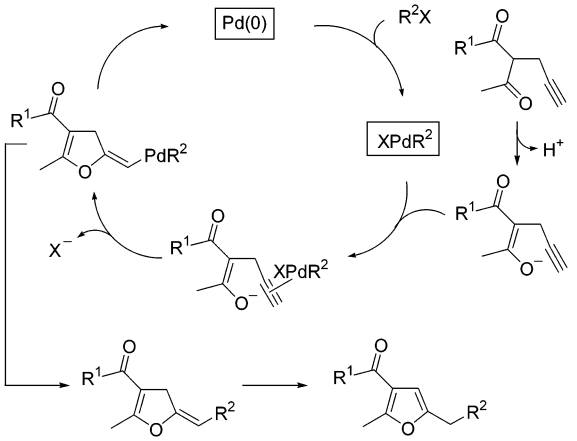
Scheme 147



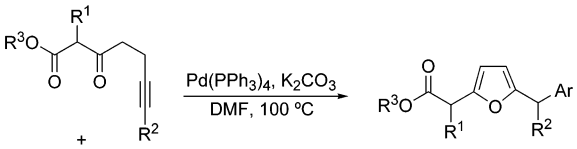
Scheme 148



Scheme 149

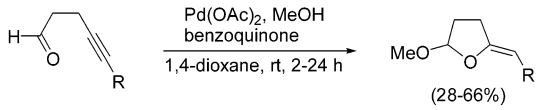


Scheme 150

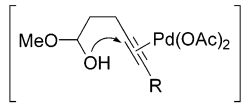


R^1 = H, alkyl
R^2 = H, aryl,
R^3 = Me, Et
X = Br, I

Scheme 151



R = Oct^n, Ph, *p*-MeC$_6$H$_4$, *p*-CF$_3$C$_6$H$_4$



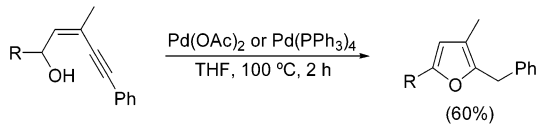
suggested intermediate

and stoichiometric *p*-benzoquinone in 1,4-dioxane at room temperature (Scheme 151). The palladium(II) catalyst apparently exhibited a dual role, activating both the carbonyl group against the MeOH attack and the alkyne moiety against the intramolecular attack of the hydroxy group. Presumably, benzoquinone acted as a ligand (and not as oxidizing agent) for the palladium catalyst. Alkenyl tetrahydrofurans were obtained in moderate yields together with small amounts of the corresponding dihydro-2*H*-pyrans, electron-withdrawing groups favoring the five-membered ring formation.

One main disadvantage of the ruthenium-catalyzed preparation of furans from (*Z*)-pent-2-en-4-yn-1-ols, reported by Dixneuf et al. (see Scheme 130), was the exclusive application to terminal alkynes. However, by using palladium compounds as catalysts, cyclization occurred in moderate yields on the alkyne moiety bearing a phenyl group (Scheme 152).[191b]

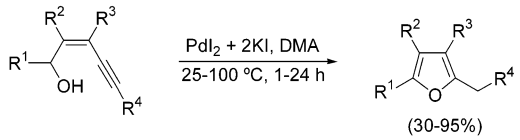
Within the same type of starting materials, Salerno et al. used a very simple catalytic system consisting of K_2PdI_4 under neutral conditions to accomplish the

Scheme 152



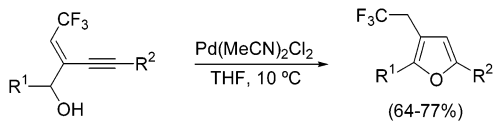
R = H, Et

Scheme 153



R^1, R^2 = H, Et, Ph
R^3 =H, Me, Et, Ph
R^4 = H, Bu^n, Ph, Me$_2$C=CH

Scheme 154



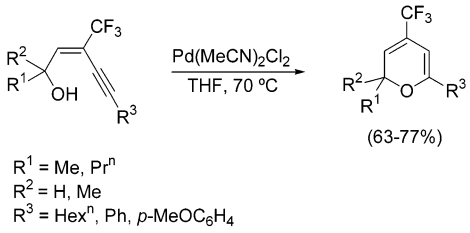
R^1 = H, Pr^n, Ph
R^2 = Hex^n, Ph, TMS

cycloisomerization of a wide variety of (*Z*)-2-en-4-ynols.[214] This methodology was very versatile, being applicable to different substitution patterns in the starting material (e.g., terminal and internal alkynes) and providing most of the corresponding furans in high yields (Scheme 153). The cycloisomerization process was proposed to follow the general mechanism for intramolecular nucleophilic attack on the palladium(II)-activated alkyne, including an *anti-exo-dig* oxypalladation, protonolysis of the resulting vinylpalladium intermediate, and acid-catalyzed aromatization. When the reaction was carried out in MeOH under 100 atm of air and CO at 70 °C, the corresponding methyl 2-(2-furyl)acetates, derived from an oxidative cyclization−alkoxycarbonylation process, were obtained in good yields (64−82%).[215]

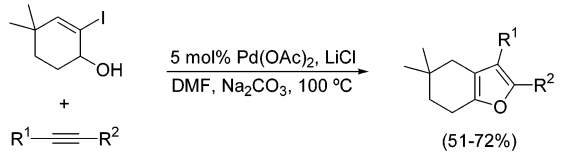
Quing et al. described a novel route to the synthesis of 3-trifluoroethylfurans by the palladium-catalyzed cyclization−isomerization of (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohols.[216] $Pd(MeCN)_2Cl_2$ and $Pd(PhCN)_2Cl_2$ complexes exhibited similar activities and good yields under very mild reaction conditions (10 °C), whereas $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $Pd(PPh_3)_2Cl_2$ were inactive under similar reaction conditions (Scheme 154). However, and in contrast to the furan syntheses shown in Schemes 152 and 153, when (*E*)-3-alkynyl-3-trifluoromethyl allylic alcohols were used as starting materials and the reactions were performed at 70 °C, a 6-*endo-dig* cyclization occurred, furnishing, apparently, the first synthesis of substituted 4-trifluoromethyl-2*H*-pyrans. It was assumed that the change in the mode of cyclization was due to the powerful electron-withdrawing character of the trifluoromethyl group (Scheme 155).[217]

Larock et al. synthesized various furans and pyrans via palladium-catalyzed coupling−annulation of appropriate hydroxy-substituted vinylic halides with internal alkynes (Scheme 156).[76] As occurred with nitrogenated starting materials (see Scheme 53), the

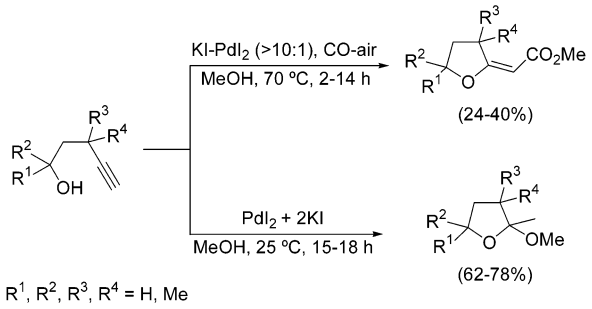
Scheme 155



Scheme 156



Scheme 157

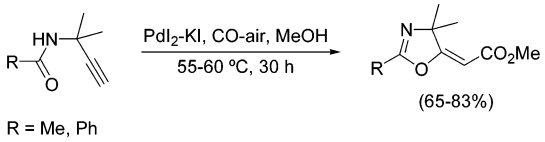


reaction proceeded regioselectively giving moderate to good yields of the products.

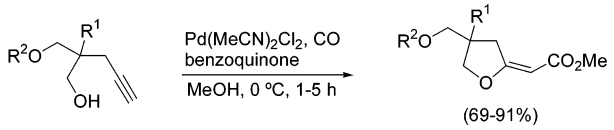
The cyclization−alkoxycarbonylation of acetylenic substrates promoted by the action of palladium catalysts has been widely used as a powerful methodology for the straightforward preparation of acetic acid derivatives bearing a heterocyclic moiety. For instance, oxidative cyclization−alkoxycarbonylation of terminal alk-4-yn-1-ols yielded (2*E*)-[methoxycarbonyl)methylidene]tetrahydrofurans when the reaction was carried out in MeOH at 70 °C and 100 atm of a 9:1 mixture of CO and air in the presence of catalytic amounts of PdI_2−KI (with large excess of KI with respect to PdI_2, >10:1) (Scheme 157).[218] However, yields were low due to the addition of methanol to the exocyclic carbon−carbon double bond and cycloisomerization followed by alcohol addition as side reactions. On the other hand, the yield of the 2-methoxy-2-methyltetrahydrofurans derived from the latter side reaction could be notably improved by decreasing the amount of KI with respect to PdI_2 to 2:1 and in the absence of CO.

The above methodology applied to 2-ynylamides afforded (*E*)-5-[(methoxycarbonyl)methylidene]oxazolines in good yields (Scheme 158).[219] Small amounts of the (*Z*)-diastereomers were detected as a result of isomerization of the (*E*)-diastereomers, the *E*-stereochemistry observed being in agreement with the anti 5-*exo*-*dig* attack of oxygen to the palladium(II) activated alkyne, followed by stereospecific oxycarbonylation reaction. Different oxazolines bearing chelating groups as well as bisoxazolines were synthesized

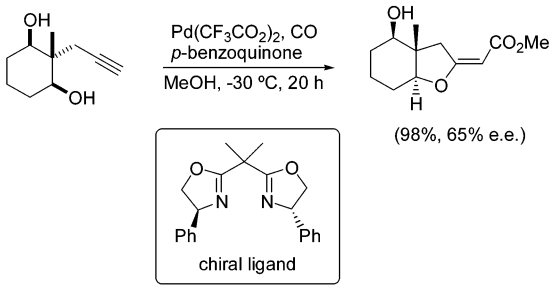
Scheme 158



Scheme 159



Scheme 160



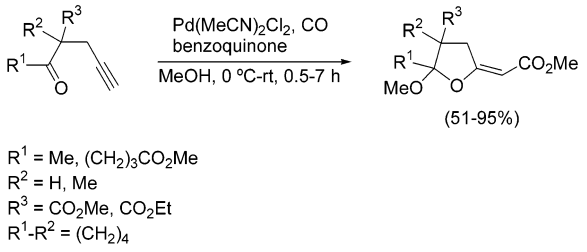
in this manner. On the other hand, acetylenic ureas gave a mixture of the corresponding oxazolines and oxazolidinones.[86]

Kato, Akita et al. made a notable contribution to this field, improving the above methodology by the introduction of *p*-benzoquinone as a very efficient proton scavenger and as an agent for the oxidative transfer of the generated Pd(0) species to a Pd(II) species. Thus, cyclic and acyclic alk-4-yn-1-ols were transformed into cyclic (*E*)-β-alkoxyacrylates, in good to excellent yields, by oxidative cyclization−methoxycarbonylation in the presence of catalytic Pd-$(MeCN)_2Cl_2$, *p*-benzoquinone, in MeOH at 0 °C under a CO atmosphere (Scheme 159).[220] Different functional groups were compatible with these reaction conditions, though the presence of a free hydroxyl group in the substrate was necessary to initiate the reaction. As a synthetic application, a new total synthesis of the antifungal (+)-cystothiazole A was presented.[221]

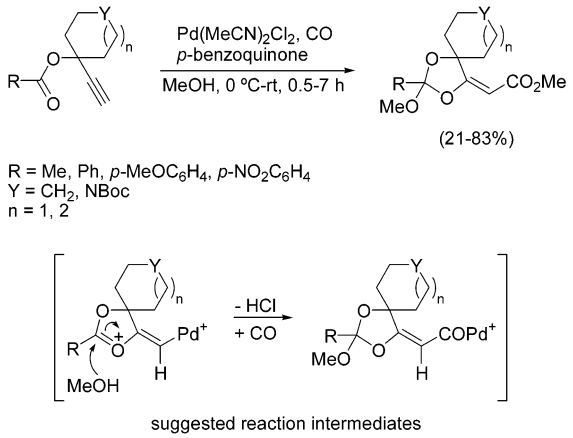
The above-described methodology was extended to the first asymmetric cyclization−carbonylation of cyclic 2-methyl-2-propargyl-1,3-diols catalyzed by palladium(II) in the presence different chiral bisoxazolines as ligands.[222] Products were obtained with excellent yields and moderate enantioselectivities, the best result obtained being shown in Scheme 160.

As a parallel and closely related work to the intramolecular cyclization of alkynyl aldehydes reported by Yamamoto et al. (see Scheme 151),[213] Kato et al. described the oxidative cyclization−carbonylation of 4-yn-1-ones under very mild reaction conditions.[223] Reactions were performed with catalytic $Pd(MeCN)_2Cl_2$ and stoichiometric *p*-benzoquinone in MeOH under a CO atmosphere at room temperature, providing the corresponding cyclic ketals in moderated to good yields (Scheme 161). In contrast to the

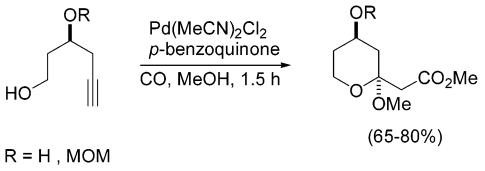
Scheme 161



Scheme 162



Scheme 163



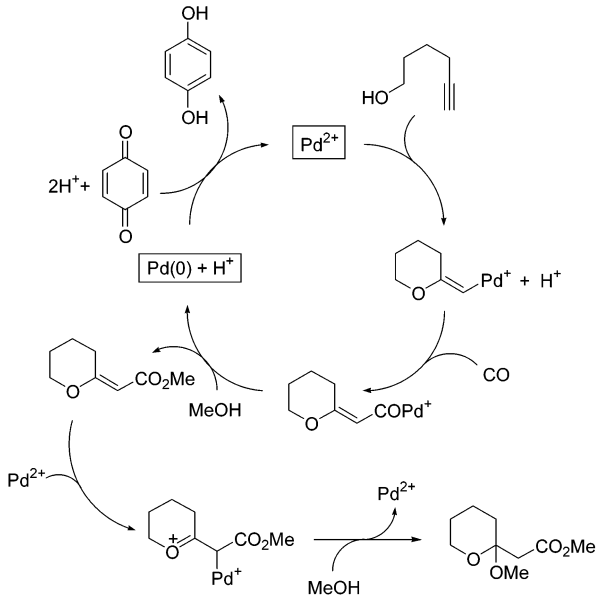
proposal by Yamamoto et al., *p*-benzoquinone was considered in this case to work as a palladium(0) reoxidizing agent rather than as a ligand.

Under similar reaction conditions but starting from propargyl acetates and benzoates, the corresponding (*E*)-cyclic ortho esters were obtained in moderate to good yields (Scheme 162).[224] No reaction was observed for internal acetylenes, whereas the presence of electron-donating groups on the benzoate moiety enhanced the reaction yield. The mechanism proposed for this process involves a vinylpalladium intermediate, which suffers nucleophilic attack of MeOH on the carbonyl group, followed by CO insertion to afford the ortho ester products.

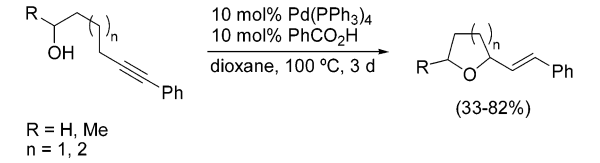
Marshall et al. applied the cyclization−alkoxycarbonylation methodology to a series of *δ*-hydroxy alkynes, which were converted into the corresponding methyl ketopyranosides with good yields and excellent stereoselectivity (Scheme 163).[225] A stepwise process involving an initial 6-*exo*-*dig* reaction followed by a kinetically controlled methanolysis was proposed to account for the formation of the products. The full catalytic cycle for this alkoxycarbonylation−alcohol addition is depicted in Scheme 164.

In a different mechanistic context, Yamamoto's methodology concerning the palladium−benzoic-acid-catalyzed intermolecular hydroalkoxylation of 1-phenylprop-1-yne (see Scheme 135) was also applied to the intramolecular version of different substrates,

Scheme 164



Scheme 165



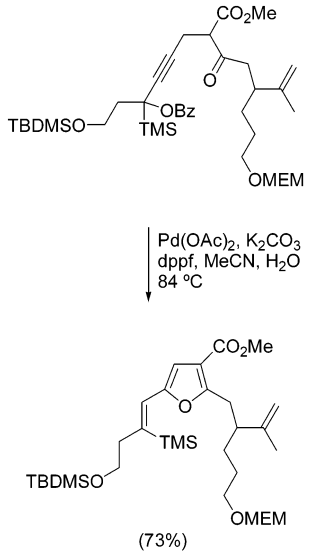
providing the corresponding five- and six-membered cyclic ethers in moderate to good yields (Scheme 165).[200] Better yields were obtained of the resulting tetrahydrofurans in comparison with the homologous tetrahydropyrans, products containing two stereocenters being obtained as a 1:1 mixture of diastereomers. A mechanism similar to that proposed for the previously described hydroamination process was suggested (see Scheme 48).

Recently, Wipf et al. accomplished the synthesis of the C1−C18 segment of the furanocembranes lophotoxin and pukalide, the key step being the palladium-catalyzed furan ring formation from an appropriate ketoalkyne (Scheme 166).[226] The high stereoselectivity of the reaction was rationalized in terms of an allene formation that isomerizes to the 2-alkenylfuran through a protonation involving the less hindered face of the allene followed by deprotonation.

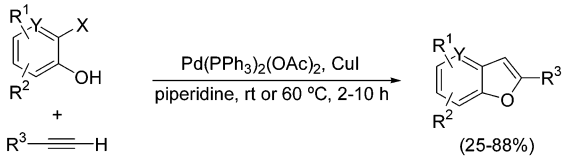
On the other hand, many research groups have focused on the palladium-catalyzed intramolecular hydroalkoxylation of 2-alkynylphenol derivatives as a very powerful tool for the construction of benzo[*b*]-furan systems and related heterocondensed compounds.[227] Pioneering work on this topic was developed by Cacchi et al., reporting the preparation of 2-substituted benzo[*b*]furans and furo[3,2-*b*]pyridines by the reaction of 2-hydroxyaryl and hydroxyheteroaryl halides with terminal alkynes, in the presence of a palladium catalyst and copper(I) iodide as cocatalyst (Scheme 167). The reactions were carried out under mild reaction conditions, being compatible with a variety of functional groups.[228]

The above strategy has been successfully exploited by different research groups. Thus, it was utilized

Scheme 166

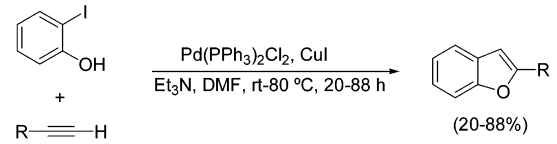


Scheme 167



R^1 = H, Me, CHO
R^2 = H, MeO
R^3 = Bu^n, Ph, CH_2OH, C(OH)(Me)Et, CH(OH)Ph, $CH(OEt)_2$, CO_2Et
1-hydroxycyclohexyl
$R^3C{\equiv}CH$ = mestranol
X = Br, I
Y = CH, N

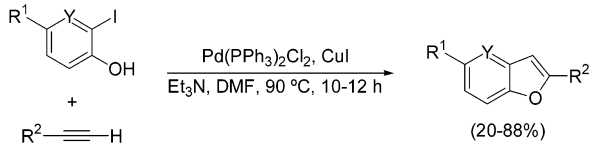
Scheme 168



R = Ph, *m*-ClC_6H_4, CH_2OH, CMe_2OH, CH(OH)CH=CHMe, CH(OH)Ph
o-MeC_6H_4CHOH, *m*-MeC_6H_4CHOH, *p*-$MeOC_6H_4CHOH$

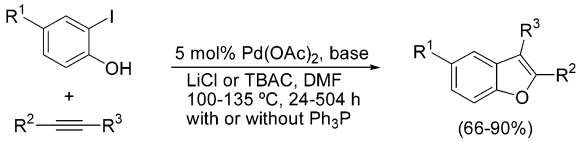
in the late 1980s by Villemin et al. to transform *o*-bromophenol into 2-phenylbenzofuran by reaction with phenylacetylene in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and Et_3N.[154] These reaction conditions were applied by Kundu et al. to the synthesis of a series of 2-substituted benzo[*b*]furans starting from *o*-iodophenol and different arylacetylenes and propargyl alcohols (Scheme 168).[229] Torii et al. introduced additional halogen atoms on the aromatic ring of the starting *o*-iodophenol or 2-iodo-3-pyridinol, also demonstrating that both the coupling and cyclization steps were cooperatively assisted by the action of the two metals [palladium(II) and copper(I)] (Scheme 169).[230] In contrast and on the basis of some base-catalyzed cyclization experiments of an *o*-alkynylphenol intermediate, Kundu et al. proposed that the cyclization step was induced by the presence of triethylamine, the corresponding phenoxide ion attacking the carbon−carbon triple bond without any metal activation.[229b] However, when the mentioned

Scheme 169



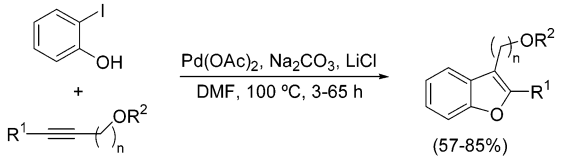
R^1 = H, Me, Cl
R^1 = I in the starting material is $R^2C{\equiv}C$ in the product
R^2 = Ph, Hex^n, CH_2OTHP, CMe_2OH, 6-methoxy-2-naphthyl
Y = CH, N

Scheme 170



R^1 = H, Ac
R^2 = Me, Ph
R^3 = Bu^t, CO_2Et, TIPS

Scheme 171



R^1 = TMS, TES, TIPS, TBDMS
R^2 = H, TES, TIPS, TBDMS

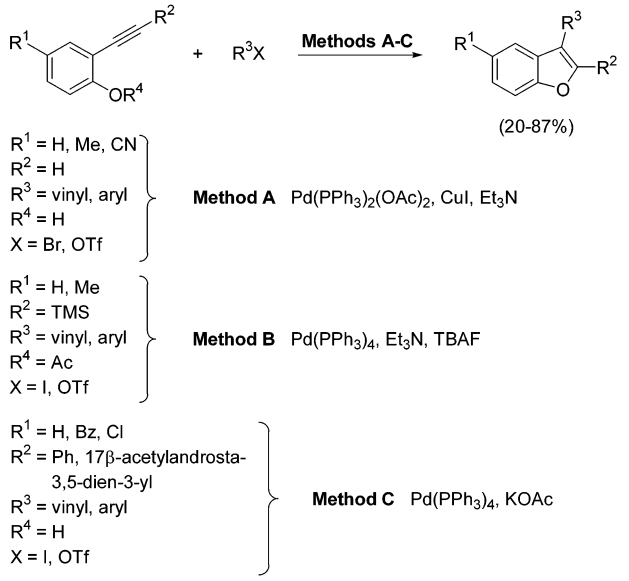
$Pd(PPh_3)_2Cl_2$−CuI−Et_3N system was applied to the coupling of a substituted *o*-iodophenol and trimethylsilylacetylene, no in situ cyclization was observed, the reaction requiring the presence of a stronger base such as TMG in refluxing toluene.[231]

The first palladium-catalyzed coupling−cyclization of *o*-iodophenols and internal alkynes seems to be that reported by Larock et al. in the mid 1990s, leading to various 2,3-disubstituted benzofurans in good to excellent yields.[146] This intramolecular hydroalkoxylation proved to be more difficult than the analogous hydroamination to generate indoles,[106] higher temperatures being required with the consequent decrease in regioselectivity. The process was limited to hindered alkyl acetylenes or acetylenes bearing aryl, carbonyl, or silyl groups (Scheme 170).

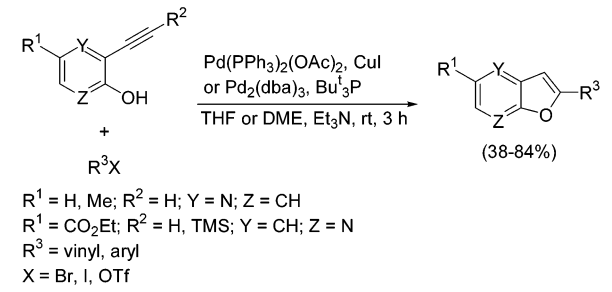
Bishop et al. synthesized a variety of 3-hydroxyalkylbenzo[*b*]furans by the palladium-catalyzed coupling−heteroannulation of silyl-protected alkynols with *o*-iodophenol (Scheme 171).[232] Propynols required silyl protection of the hydroxy group to avoid a side reaction leading to 1-oxa-2-silacyclopent-3-enes, resulting from the reaction of the free hydroxy group on silicon in the intermediate vinylpalladium species. However, *O*-protection was not essential for butynols and pentynols, where formation of the corresponding six- or seven-membered 1-oxa-2-silacycloalkenes is less favored. In general, the regioselectivity of the process was high, only 2−10% of the regioisomeric benzofurans being obtained.

The synthesis of differently substituted benzo[*b*]furans through the palladium-catalyzed annulation methodology followed by reaction with unsaturated

Scheme 172



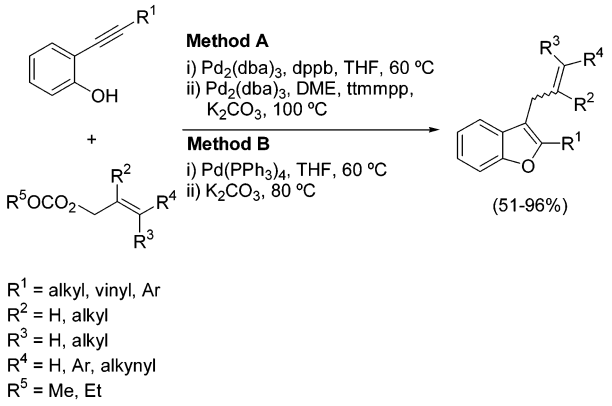
Scheme 173



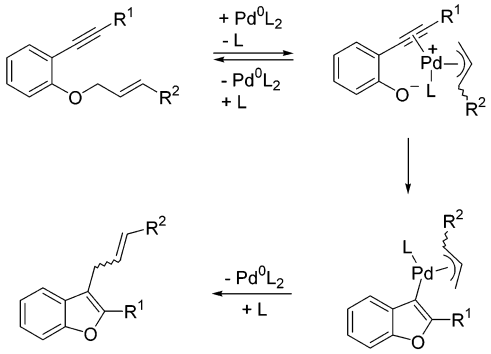
halides or triflates was widely studied by Arcadi and Cacchi et al. Thus, the reaction of *o*-ethynylphenols with aryl halides or aryl and vinyl triflates in the presence of $Pd(PPh_3)_2(OAc)_2$, CuI, and Et_3N afforded the corresponding 2-vinyl and 2-arylbenzo[*b*]furans (method A, Scheme 172).[233] Alternatively and in order to prevent the formation of byproducts, *o*-[(trimethylsilyl)ethynyl)]phenyl acetates were used as starting materials in the presence of $Pd(PPh_3)_4-Et_3N-TBAF$ or $Pd(PPh_3)_4-KOBu^t$ (method B, Scheme 172). The use of *o*-alkynylphenols with an internal alkyne moiety in the presence of $Pd(PPh_3)_4-KOAc$ (method C, Scheme 172) furnished 2,3-disubtituted-benzo[*b*]-furans through an annulation promoted by *σ*-vinyl- and *σ*-arylpalladium complexes generated in situ, whereas under a CO atmosphere 2-vinyl- and 2-aryl-3-acylbenzo[*b*]furans were obtained in low to moderate yields.

The above methodology was applied to the reaction of 2-ethynyl-3-pyridinols and 3-ethynyl-2-pyridinols with a variety of aryl and heteroaryl halides or vinyl triflates in the presence of any of the two catalytic systems $Pd(PPh_3)_2Cl_2-CuI$ or $Pd_2(dba)_3-Bu^t{}_3P$.[234] The expected 2-substituted furo[3,2-*b*]pyridines and 2-substituted furo[2,3-*b*]pyridines were obtained in moderate to good yields, in some cases together with variable amounts of 2-unsubstituted furopyridines and bifuropyridines (Scheme 173). Alternative approaches to the synthesis of furopyridines were suggested based on the palladium-catalyzed reaction of (trimethylsilylethynyl)pyridinols with organic halides or by coupling–cyclization of iodopyridinols and trimethylsilylacetylene.

Scheme 174



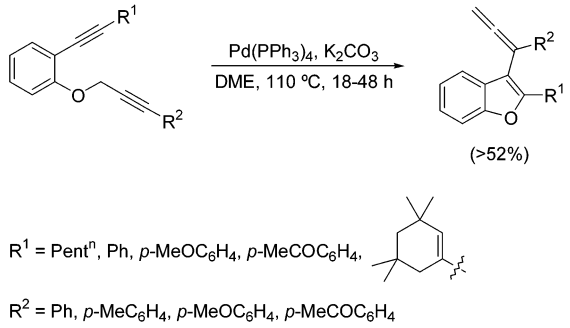
Scheme 175



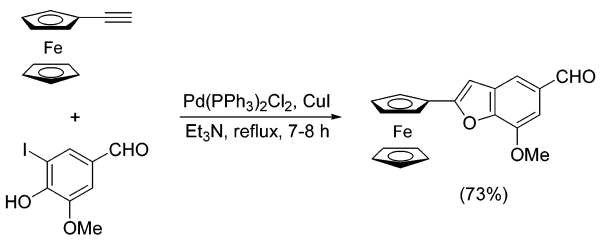
The same research group developed two different protocols for the preparation of 2-substituted-3-allylbenzo[*b*]furans from *o*-alkynylphenols and allyl carbonates under palladium catalysis (Scheme 174).[235] The stepwise method (method A) was based on the preparation of stereo- and regioisomeric mixtures of *O*-allyl derivatives and their subsequent cyclization to benzo[*b*]furans, being the method of choice when steric differences between the two allylic termini are small. The one-pot protocol (method B), omitting isolation of the *O*-allyl derivatives, was employed when the reaction proceeds through η^3-allylpalladium complexes and also when the two allylic termini are markedly different from a steric point of view. Concerning the reaction mechanism, the cyclization of the *O*-allyl derivatives was suggested to proceed through the palladium-promoted ionization of the allylic C–O bond and displacement of one ligand to the palladium by the carbon–carbon triple bond, intramolecular nucleophilic attack of the oxygen atom across the activated carbon–carbon triple bond, and reductive elimination (Scheme 175).

Identical work was published at the same time by Balme et al. using $Pd(PPh_3)_4$ as catalyst in a mixture of MeCN–THF at 80 °C.[236] In general, longer reaction times were needed for allyl fragments bearing a substituent on the central carbon. The stereochemistry of the allylic moiety in the product was found to be exclusively *E*, whereas in Cacchi's report about 10% of the (*Z*)-diastereomer was also obtained. Under these reaction conditions, 2-alkynylphenols reacted with tertiary propargyl carbonates giving 2-substi-

Scheme 176



Scheme 177



tuted 3-allenyl benzo[*b*]furans in relatively low to good yields (15−77%).[237] Unfortunately, substantial amounts of the undesired 2-substituted benzo[*b*]-furans (without bearing the allenyl moiety) were obtained as byproducts (11−32%).

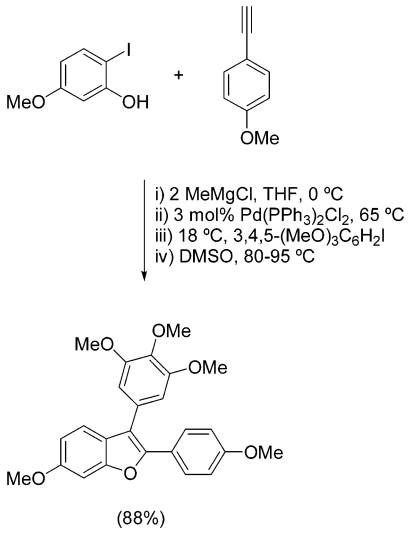
The above methodology reported by Cacchi's group was extended to propargylic *o*-(alkynyl)phenyl ethers, which in the presence of $Pd(PPh_3)_4$ and K_2CO_3 at higher temperature (110 °C) afforded 2-substituted-3-allenylbenzo[*b*]furans in good yields (Scheme 176).[238] Variable amounts of the corresponding 2-substituted-3-propargylbenzo[*b*]furans were also obtained depending on the nature of the starting alkyne. A similar mechanistic rationale to that mentioned above was proposed but involving allenylpalladium species.

More recently, ferrocenylacetylene was coupled and cyclized by the reaction with 5-iodovanillin in the presence of $Pd(PPh_3)_2Cl_2$−CuI, giving the corresponding benzo[*b*]furan in good yield (Scheme 177).[116]

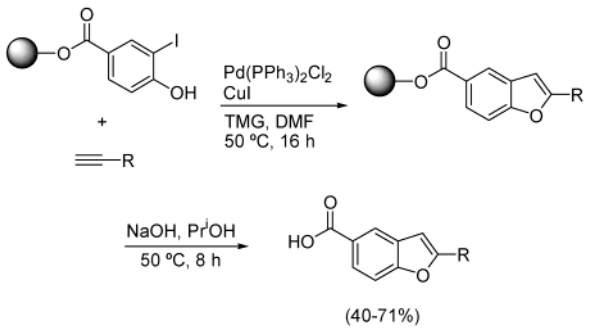
Flynn et al. described a palladium-mediated one-pot, multicomponent coupling process as direct access to 2,3-disubstituted benzo[*b*]furans.[117] The procedure utilized involves initial deprotonation of a mixture of an *o*-iodophenol derivative and a terminal acetylene with 2 equiv of MeMgCl at 0 °C, addition of $Pd(PPh_3)_2Cl_2$ and heating at 65 °C to give the coupling product, and final dilution with DMSO and addition of an organic halide followed by heating (Scheme 178). Alkenyl bromides, alkenyl iodides, aryl iodides, allyl acetate, and propargyl tosylate proved to be effective coupling partners in this heteroannulation process, which in combination with CO allowed the carbonylative cyclization. These products exhibited certain activity both as tubulin polymerization inhibitors and as cytotoxins.[118]

Consecutively to the already commented Bedeschi's solid-phase synthesis of 2-substituted indoles (see Scheme 88),[126] this group reported the synthesis of 2-substituted benzofuran carboxylic acids by the palladium-catalyzed coupling−heteroannulation of

Scheme 178



Scheme 179



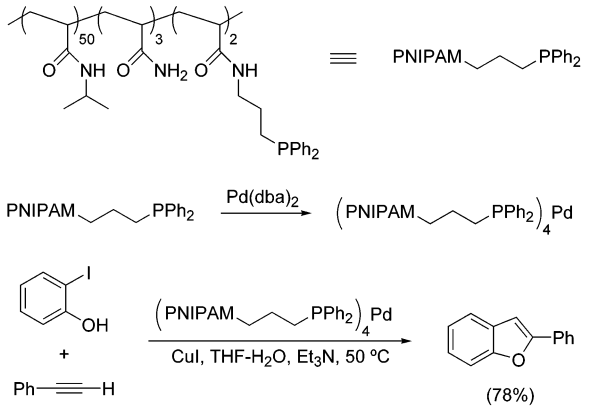
R = Hexn, But, Ph, $(CH_2)_3Cl$, $(CH_2)_3OH$, $C(OH)Me_2$, CH_2NH_2, CH_2NEt_2, $CH_2NHCONHBu^t$, $CH_2NHCO_2Bu^t$

4-hydroxy-3-iodobenzoic acid and terminal alkynes under similar reaction conditions.[239] The expected benzofurans were obtained in 40−71% overall yield after cleavage of the TentaGel-S resin in basic medium (Scheme 179). Although yields were lower with respect to the reaction performed with the non-polymer-bound 4-hydroxy-3-iodobenzoic acid methyl ester (67−90%), this mild method is potentially promising for the creation of combinatorial chemistry libraries of this type of organic compounds.

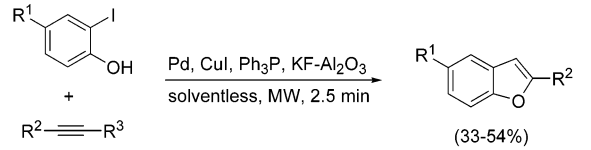
Bergbreiter et al. explored the utility of linear poly(*N*-isopropylacrylamide) (PNIPAM) polymers which possess the peculiarity of being soluble in cold water but insoluble in hot water.[240] The reaction of the phosphine-containing PNIPAM support with $Pd(dba)_2$ provided the corresponding supported Pd(0) catalyst. This catalyst was effective in the reaction of 2-iodophenol with phenylacetylene to furnish the expected benzofuran product (Scheme 180). In addition, the catalyst could be reused up to 15 times with little loss of activity.

The formation of 2-substituted benzo[*b*]furans in a solventless, microwave-enhanced reaction medium was studied by Kabalka et al. A one-pot Sonogashira coupling−cyclization of *o*-iodophenol derivatives and terminal alkynes in the presence of potassium fluoride doped with alumina, palladium powder, copper(I) iodide, and triphenylphosphine led to the corresponding benzofurans in moderate yields (Scheme

Scheme 180

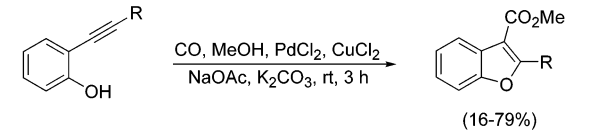


Scheme 181



R^1 = H, Me, COMe
R^2 = Hex^n, Oct^n, Ph, *p*-MeC_6H_4, *o*-FC_6H_4, *p*-BrC_6H_4
R^3 = H, TMS

Scheme 182



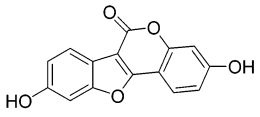
R = Bu^n, Ph, CO_2Et

181).[135] 1-Substituted-2-(trimethylsilyl)acetylenes also reacted under the above conditions following a desilylation−coupling−cyclization sequence. Alternatively, 2-substituted benzo[*b*]furans were synthesized also in moderate yields from *o*-ethynylphenol or *o*-[(trimethylsilyl)ethynyl]phenol by coupling−cyclization with various aryl and vinyl iodides under the same reaction conditions.

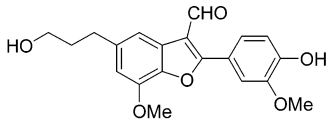
The palladium-catalyzed carbonylative cyclization of *o*-alkynylphenols has proven to be a useful method for the synthesis of benzo[*b*]furan-3-carboxylates.[241] Pioneering work on this field was carried out by Yamanaka et al., who described the successive cyclization−carbonylation of *o*-ethynylphenol derivatives in the presence of palladium(II) chloride, carbon monoxide, and methanol (Scheme 182). The low yield obtained in the carbonylative cyclization of 2-(hydroxyphenyl)propiolate (16%) was attributed to the weak coordination of the palladium(II) species to the relatively electron-poor carbon−carbon triple bond. A reaction mechanism similar to that depicted in Scheme 74 was proposed to account for the formation of the corresponding benzo[*b*]furan-3-carboxylates.[103]

This methodology found application to the synthesis of 2-(4-hydroxy-2-methoxyphenyl)-6-methoxybenzofuran-3-carboxylic acid methyl ester and coumestrol, both isolated from alfalfa, the latter showing estrogenic activity (Chart 3).[242] Under similar reaction conditions, Scammells et al. successfully accomplished the synthesis of the natural product XH-14 (from the plant *Salvia miltiorrhiza*), a potent antagonist of the A_1 adenosine receptor (Chart 3),[243] as well as the synthesis of 2-substituted analogues of XH-14.[244]

Chart 3

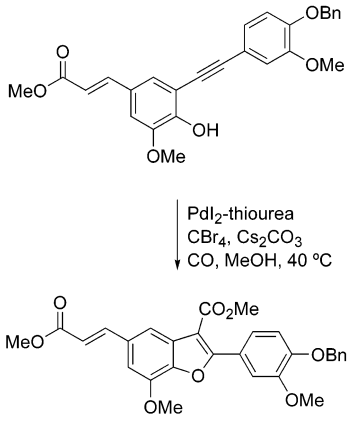


coumestrol



XH-14

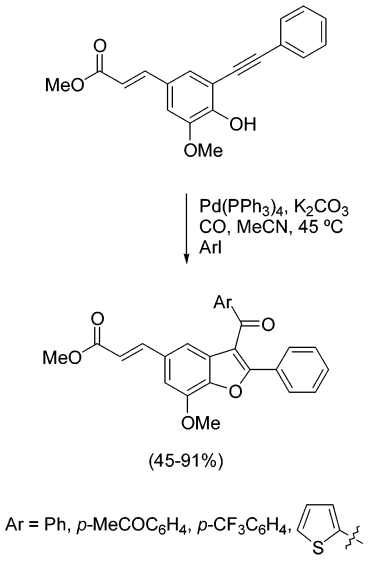
Scheme 183



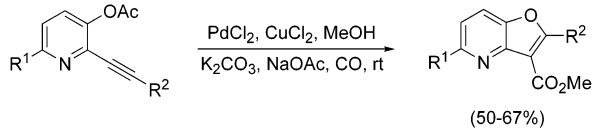
The above methodology was complemented by the research of Yang et al. with the cocatalytic system PdI_2–thiourea, allowing the carbonylative cyclization of both electron-rich and electron-deficient substrates under mild reaction conditions (CBr_4 and Cs_2CO_3 in MeOH at 40 °C and balloon pressure of CO) (Scheme 183).[245] As a novelty, CBr_4 was introduced for the first time as an oxidative agent for the turnover of palladium(0) to palladium(II), the corresponding benzo[*b*]furan-3-carboxylates being obtained in very good yields (78−85%). Although noncatalytic but in connection with this work, a 90-membered 2,3-disubstituted benzo[*b*]furan library was designed through a palladium(II)-mediated cascade carbonylative annulation of *o*-alkynylphenols on silyl-linker-based macrobeads.[246] In this case, a stoichiometric amount of $Pd(PPh_3)_2Cl_2$−dppp (1:1) in combination with CsOAc, CO, and the phenol in DMF at 45 °C proved to be effective, 70 of the benzo[*b*]furan-3-carboxylates being obtained in over 90% purity after 48 h.

When the above-depicted reaction was effected in the presence of an aryl iodide (in the absence of MeOH) and in a modified catalytic system containing palladium(0), the corresponding 2-substituted-3-aroylbenzo[*b*]furans were obtained in moderate to good yields, aryl iodides substituted with electron-donating groups giving better yields than those bearing electron-withdrawing groups (Scheme 184).[247]

Scheme 184

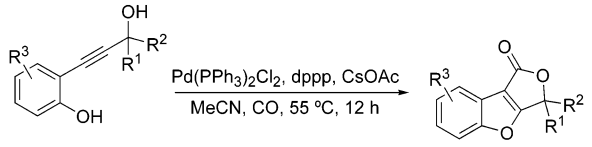


Scheme 185



R^1 = H, Me
R^2 = Bu^n, Ph, $CH(OEt)_2$, COH(Me)Et

Scheme 186



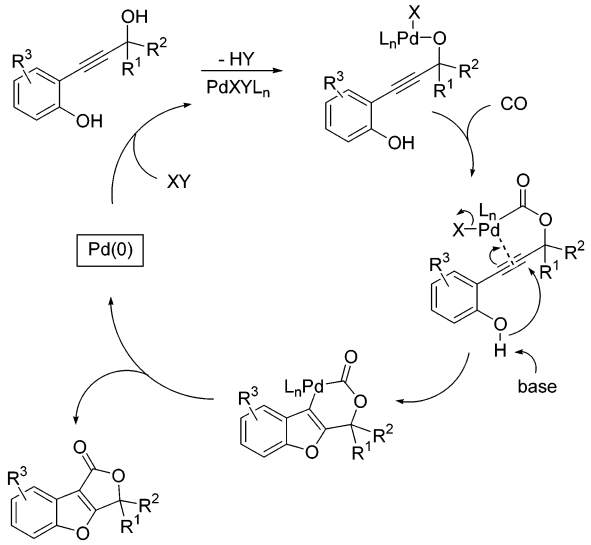
R^1 = H, alkyl, aryl
R^2 = alkyl, aryl
R^1-R^2 = cyclic moiety
R^3 = H, OMe, OH, $TBDMSCH_2OCH_2$
$TBDMS(CH_2)_2NHCO$

From some mechanistic studies it was inferred that the process involves coordination of cationic and less hindered acylpalladium complexes with the *o*-alkynylphenol to promote the intramolecular nucleophilic addition, followed by reductive elimination.

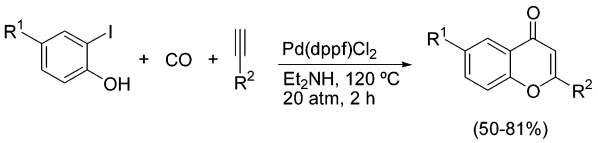
A series of 2,3-disubstituted furo[3,2-*b*]pyridines and 2,3-disubstituted furo[2,3-*c*]pyridines were readily prepared by Arcadi and Cacchi et al. through a palladium-catalyzed carbonylative annulation of *o*-acetoxyalkynylpyridines (Scheme 185).[248] Reactions were carried out with $PdCl_2$ in MeOH under a balloon of CO in the presence of NaOAc and K_2CO_3 as the bases and $CuCl_2$ as the oxidative agent.

When *o*-alkynylphenols containing a propargyl alcohol moiety were subjected to the palladium(II)-catalyzed carbonylative annulation reaction, benzo[*b*]furo[3,4-*d*]furan-1-ones were obtained in good yields as very structurally interesting and common naturally occurring scaffolds (Scheme 186).[249] In general, those substrates containing five-membered rings (on the alkyne moiety) or tertiary propargyl alcohols gave higher yields than those containing six-membered rings or secondary propargyl alcohols, respectively. A reaction mechanism was proposed for this carbonylative cyclization involving alcohol attack on the palladium(II) species followed by CO insertion, intramolecular nucleophilic addition of phenoxide to the resulting acylpalladium complex, and reductive elimination with subsequent palladium(0) oxidation (Scheme 187).

Scheme 187



Scheme 188



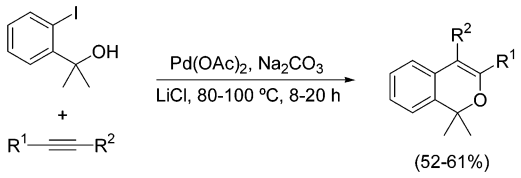
R^1 = H, Me
R^2 = $Pent^n$, Ph, p-$MeOC_6H_4$,
S

Some other interesting benzofused oxygen-containing heterocycles have also been prepared by intramolecular hydroalkoxylation of different types of substrates. For instance, in the early 1990s Kalinin et al. reported the carbonylative coupling−cyclization of *o*-iodophenols and terminal acetylenes in the presence of a palladium catalyst, affording a series of flavones and chromones in a one-pot process (Scheme 188).[250,137b] Aryl-, heteroaryl-, and alkylacetylenes gave the corresponding 2-substituted chromones under relatively harsh reaction conditions (120 °C, 20 atm) but in good yields, taking into account that the reaction was performed in one pot.

The methodology developed by Larock et al. on the synthesis of benzofused heterocycles via palladium-catalyzed annulation of internal alkynes also proved to be effective in the synthesis of 1*H*-isochromene derivatives starting from *o*-iodobenzylic alcohols and alkyl-, aryl-, or carbonyl-containing internal alkynes (Scheme 189).[146]

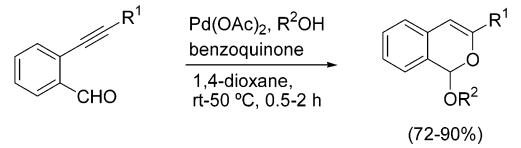
1*H*-Isochromenes were also prepared by Yamamoto et al. by extension of the previously described methodology for the synthesis of cyclic aliphatic alkenyl ethers (Scheme 151) to starting aryl acetylenic aldehydes.[213] The reaction was performed with catalytic $Pd(OAc)_2$, stoichiometric *p*-benzoquinone, and 2 equiv

Scheme 189



R^1 = Bu^t; R^2 = Me
R^1 = Ph; R^2 = CO_2Et, C(OH)Me_2

Scheme 190



R^1 = Ph, Bu^n, TMS
R^2 = Me, Et, Pr^i

of the alcohol in 1,4-dioxane at room temperature (Scheme 190). Methyl, ethyl, and isopropyl alcohol gave high yields of the expected 1*H*-isochromenes, a low yield (22%) being only observed for the terminal-alkyne-containing starting derivative.

3.3. Other Catalysts

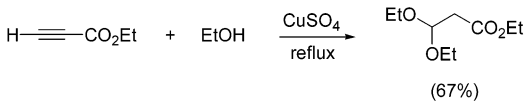
3.3.1. Copper

To the best of our knowledge there is only one example of copper-catalyzed intermolecular hydroalkoxylation of alkynes, reported by Bertz et al. in the early 1990s. In this publication, the preparation of ethyl 3,3-diethoxypropionate was notably improved with respect to other methods by copper(I)-triflate-catalyzed addition of ethanol to ethyl propiolate.[251] Although the presence of the intermediate ethyl 3-ethoxyacrylate was found to depend on the reaction conditions, it could be transformed into the desired product by reaction with sodium ethoxide. On the other hand, only 3,3-diethoxypropionate and no ethyl 3-ethoxyacrylate was obtained when the reaction was performed with copper(II) sulfate (10 mol %) in refluxing ethanol followed by aqueous workup (Scheme 191).

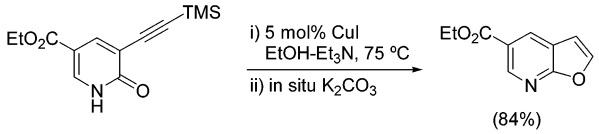
Regarding intramolecular hydroalkoxylation, the synthesis of benzofurans and related compounds accomplished by Castro et al. in the 1960s by the coupling−cyclization of *o*-iodophenol and *o*-iodobenzyl alcohol with copper(I) acetylides is well known.[152,153,252] This methodology was extended by others using *o*-iodophenols and terminal acetylenes in the presence of stoichiometric amounts of copper(I) oxide[253] or copper(I) *tert*-butoxide.[254]

The first copper-catalyzed approach to the synthesis of benzofuran derivatives was reported by Houpis et al.[255] This group transformed an alkynyl pyridone into the corresponding furopyridine with 5 mol % CuI in EtOH−Et_3N at 75 °C, removal of the TMS group

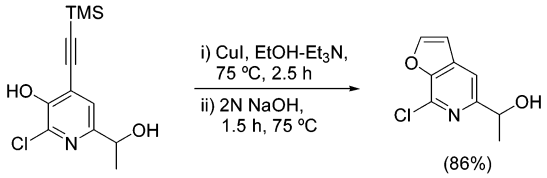
Scheme 191



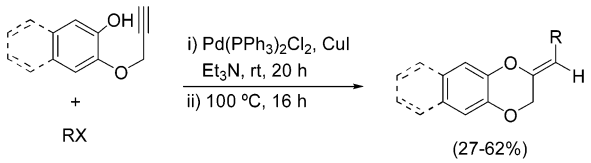
Scheme 192



Scheme 193



Scheme 194



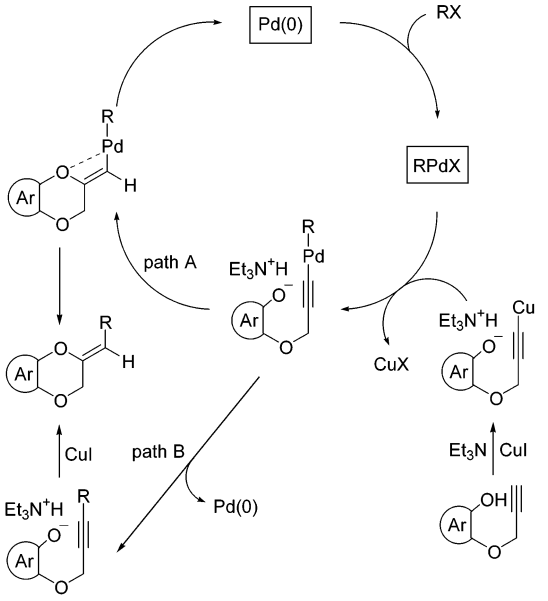
R = Ar, heteroaryl, PhCH=CH
X = Br, I

being achieved by treatment with finely powdered K_2CO_3 (Scheme 192). This furopyridine was a key intermediate in the synthesis of the HIV-protease inhibitor L-754,394.

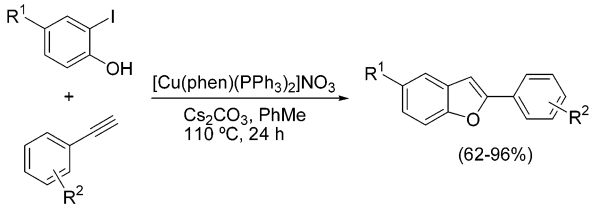
Under the same above reaction conditions, Morris et al. transformed a 4-acetylenic pyridine into the corresponding furo[2,3-*c*]pyridine in high yield, the latter being a key intermediate in the synthesis of the HIV-1-reverse transcriptase inhibitor PNU-142721 (Scheme 193).[256]

Kundu et al. found that 2-(2-propynyloxy)phenol and 3-(2-propynyloxy)-2-naphthol underwent coupling and heteroannulation with aryl halides under palladium−copper catalysis, providing a series of (*Z*)-2,3-dihydro-2-(ylidene)-1,4-benzo- and naphthodioxines in a regio- and stereoselective manner (Scheme 194).[257] A wide variety of aryl, heteroaryl, and alkenyl halides possessing different functional groups were successfully employed, the reaction being favored for aryl halides bearing electron-withdrawing groups in comparison with those bearing electron-donating groups. A very interesting and totally regio- and stereoselective bisannulation process occurred by using aromatic and heteroaromatic diiodides. A reaction mechanism was suggested involving oxidative addition of Pd(0) to the aryl halide, forming a σ-arylpalladium(II) complex and transmetalation by organocopper species to form another palladium intermediate. The latter would undergo nucleophilic attack by phenoxide or naphthoxide ion leading to a cyclic vinylpalladium species (through path A) in which Pd(II) would be stabilized by coordination with an oxygen atom. Finally, reductive elimination would furnish the 1,2-benzodioxane derivative with *Z* stereochemistry. Alternatively, path B was proposed in which cyclization would take place by the assistance of CuI and Et_3N. From experimental results, the feasibility of the Pd(0) and Pd(II)-catalyzed cyclization was discarded in favor of a cooperative action of CuI and Et_3N (Scheme 195).

Scheme 195

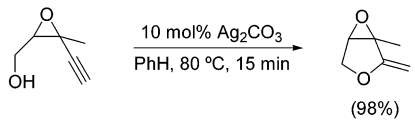


Scheme 196



R^1 = Me, Bu^t, Ph, Cl, Br, CN
R^2 = OMe, CN, COMe, CO_2Me, CH_2=CH

Scheme 197



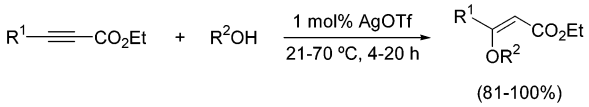
More recently, Venkataraman et al. developed a synthetic protocol of 2-arylbenzo[*b*]furans from *o*-iodophenols and aryl acetylenes using [Cu(phen)-$(PPh_3)_2$]NO_3 as catalyst and Cs_2CO_3 as base (Scheme 196).[258] Both electron-rich and electron-poor aryl acetylenes found application in this reaction, which in addition tolerated some base-sensitive functional groups, furnishing the products in good to excellent yields.

3.3.2. Silver

One example of silver-catalyzed intramolecular hydroalkoxylation of a 4-alkyn-1-ol was reported by Pale et al. (Scheme 197).[259] The reaction proceeded very fast and in excellent yield, proving to be highly regioselective, the only product obtained arising from a 5-*exo*-*dig* addition. However, a stoichiometric amount of the silver salt was needed for the corresponding trialkylsilyl acetylenic derivative.

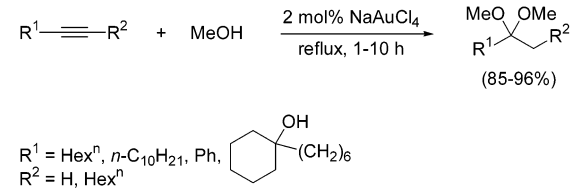
More recently, Tani et al. observed that silver(I) triflate was an efficient catalyst for the stereo- and regioselective intermolecular addition of alcohols to alkynes activated by ester groups.[260] A variety of alcohols were found to react with dimethyl acetylenedicarboxylate at 70 °C in the presence of 1 mol % AgOTf to afford the corresponding vinyl ethers resulting from a *trans*-addition (Scheme 198). Less hindered alcohols gave (*Z*)-vinyl ethers in good yields, whereas the bulkier alcohol Bu^tOH reacted very slowly, the resulting *tert*-butyl vinyl ether suffering easy hydrolysis leading to dimethyl oxalacetate. The methodology also found application to the addition of MeOH to the terminal alkyne methyl propynoate, though the internal alkyne ethyl 2-tridecynoate led to a mixture of products.

Scheme 198



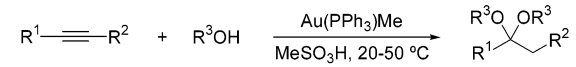
R^1 = H, CO_2Et
R^2 = Me, Et, Pr^i, Bn

Scheme 199



R^1 = Hex^n, *n*-$C_{10}H_{21}$, Ph,
R^2 = H, Hex^n

Scheme 200



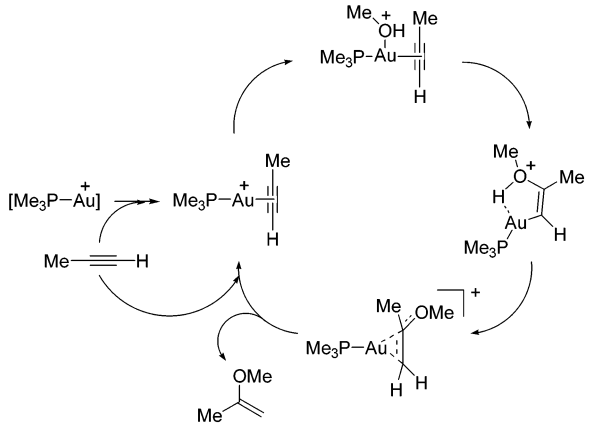
R^1 = Me, Et, Ph
R^2 = H, Et, Pr^i, Ph
R^3 = Me, Et, Pr^i, allyl

3.3.3. Gold

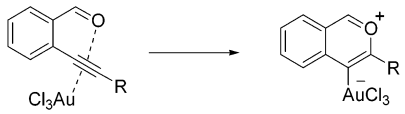
Utimoto et al. described the direct transformation of alkynes into dimethyl acetals by the addition of methanol catalyzed by sodium tetrachloroaurate (Scheme 199).[261] The reaction applied to terminal and internal alkynes gave excellent yields of the products in short reaction times (1 h for terminal and 10 h for internal alkynes)

Teles et al. used methyl(triphenylphosphine)gold-(I) and methanesulfonic acid (cocatalyst) as precursors for the in situ generation of the catalyst in the addition of alcohols to differently substituted alkynes under mild reaction conditions (Scheme 200).[262] The catalyst achieved TON of up to 10^5 and TOF of up to 5400 without being water or air sensitive. With internal symmetrical alkynes, the corresponding acetals were formed, unsymmetrical and terminal alkynes leading to addition products exclusively at the more substituted carbon atom. The reactivity of the substrates was found to increase with increasing electron density of the carbon−carbon triple bond and decreasing steric hindrance. The reactivity of the alcohols decreased by a factor of 10 when going from primary to secondary alcohols, tertiary alcohols and phenols being unreactive. A reaction mechanism was proposed based on experimental and ab initio calculations including (a) formation of a cationic gold(I) complex by protonolysis of the starting methylgold complex, (b) nucleophilic attack of the alcohol onto

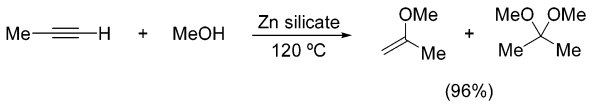
Scheme 201



Scheme 202



Scheme 203



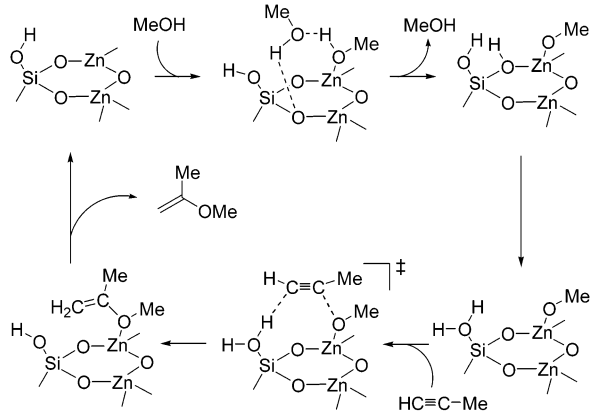
the activated gold(I) propyne complex through an associative mechanism involving coordination of methanol to gold, (c) rearrangement of the resulting complex by deprotonation at oxygen with reprotonation at carbon or by a 1,3-hydrogen migration, and (d) final ligand exchange to produce again the gold−alkyne complex (Scheme 201).

Recently, Yamamoto et al. described a $AuCl_3$-catalyzed formal [4+2] benzannulation between *o*-alkynylbenzaldehydes and alkynes to produce naphthyl ketones in good to high yields. The key step of this process was the nucleophilic attack of the carbonyl oxygen to the gold(III)-activated alkyne to form an intermediate auric ate complex (the heterodienic component) that was trapped with a series of alkynes (Scheme 202).[263]

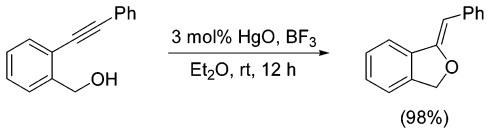
3.3.4. Zinc

Teles et al. developed very efficient heterogeneous catalysts based on zinc silicates for the intermolecular addition of primary alcohols to alkynes and allenes.[264] Among the different catalysts tested, hemimorphite and amorphous zinc silicate exhibited remarkable selectivity in the addition of methanol to propyne, providing 2-methoxypropene and 2,2-dimethoxypropane in a ratio strongly depending on the reaction conditions (Scheme 203). Using ab initio calculations an energetically plausible reaction pathway was suggested starting with coordination of a methanol molecule to a zinc atom with a vacant coordination site. Then a hydrogen transfer would take place promoted by a second methanol molecule, a proton being first transferred to the bridging oxygen and in a second step to the silanol moiety. The resulting intermediate would have the appropriate geometry to react with propyne and form 2-methoxypropene coordinated to the zinc center. Final desorption of the product would regenerate the catalytic species (Scheme 204).

Scheme 204



Scheme 205



3.3.5. Mercury

The alkoxymercuration−demercuration of alkynes in the presence of alcohols has been known since the first quarter of the 20th century and has provided a direct approach to the synthesis of vinyl ethers.[265] However, as already mentioned in the introduction to hydroamination processes, most of the research work involved stoichiometric or substantial amounts of mercury(II) salts, the reason for which these methods have been practically banned.[266]

On the other hand, a better yield than in the stoichiometric mercuration was observed by Villemin et al. in the transformation of 2-hydroxymethyldiphenylacetylene into (*Z*)-1-benzylidenedihydroisobenzofuran by treatment with catalytic mercury(II) oxide in the presence of boron trifluoride (Scheme 205).[154] The reaction took place under very mild conditions and with excellent yield.

4. Hydro-oxycarbonylation

The catalytic addition of carboxylic acids to alkynes is of paramount importance primarily for the large-scale production of industrially useful simple compounds such as vinyl acetate, monomer precursor of poly(vinyl acetate) and poly(vinyl alcohol).[172] Vinyl acetate was originally prepared by addition of sodium acetate to acetylene catalyzed by zinc acetate on charcoal at about 200 °C, though at present the most common method is a modification of the Wacker reaction with a $PdCl_2$−$CuCl_2$ catalyst.[267] However, still there is no general method for the effective catalytic addition of carboxylic acids to alkynes. It is worth noting that the most significant achievements in this field have been attained using ruthenium complexes as precatalysts, mainly for intermolecular processes, whereas palladium catalysts have found wide application for intramolecular reactions.

4.1. Ruthenium Catalysts

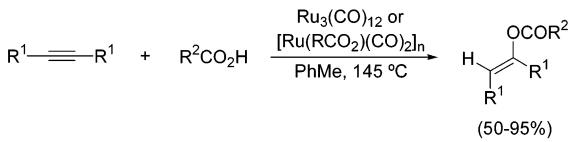
The wide scope and application of the addition of carboxylic acids to alkynes using ruthenium catalysts is reflected in the numerous reviews which appeared in the literature covering or including this subject.[268]

Pioneering work on the ruthenium-catalyzed intermolecular addition of carboxylic acids to alkynes was done was Shvo et al. using $Ru_3(CO)_{12}$ as well as $[Ru(RCO_2)(CO)_2]_n$ as catalysts.[269] Both electron-poor and -rich internal alkynes were found to react, the rate of conversion roughly following the order of acidity of the acid used. The expected vinyl esters were mainly obtained as the (*E*)-isomers as a result of stereospecific kinetically controlled *syn*-addition of the carboxylic acid to the carbon−carbon triple bond (Scheme 206). On the other hand, the regioselectivity of the addition seemed to be quite poor for unsymmetrically substituted alkynes, and a rearranged product was additionally formed in reactions with diphenylacetylene.

Mitsudo, Watanabe et al. reported the reaction of α,*β*-unsaturated carboxylic acids with terminal alkynes in the presence of a catalytic amount of bis(η^5-cyclooctadienyl)ruthenium−Bu^n_3P [$Ru(\eta^5\text{-cod})_2$−Bu^n_3P] in benzene at 80 °C, furnishing the corresponding Markovnikov enol esters with high regioselectivity (Scheme 207).[270] The reaction also worked for a *β*,*γ*-unsaturated carboxylic acid and benzoic acid. A reaction pathway was suggested involving the formation of a hydrido(carboxylate)ruthenium(IV) complex [by oxidative addition of the carboxylic acid to the Ru(II) complex], followed by insertion of the alkyne into the Ru−H bond and reductive elimination.

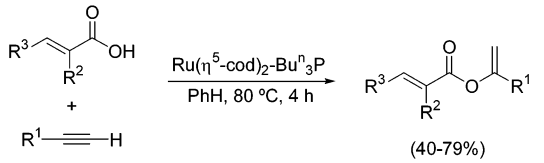
Under the above-described reaction conditions, saturated carboxylic acids did not react with alkynes. However, modification of the catalytic system by introduction of maleic anhydride as electron-deficient *π*-acid ligand allowed the addition of a wide range of saturated carboxylic acids, providing the corresponding enol esters in moderate to excellent yields and with high regioselectivity (Scheme 208).[271] Maleic anhydride was not required in the addition of α,*β*-unsaturated carboxylic acids and benzoic acid since a role as *π*-acid ligands was played by themselves.

Scheme 206



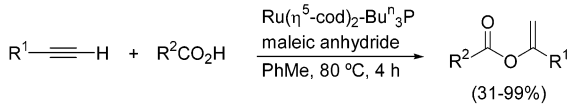
R^1 = Pr^n, Ph, CO_2Me
R^2 = Me, Me_3C, Ph, *p*-MeC_6H_4, *p*-FC_6H_4

Scheme 207



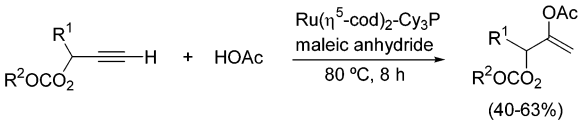
R^1 = Pr^n, Bu^t
R^2 = H, Me
R^3 = H, Me, (*E*)-MeCH=CH

Scheme 208



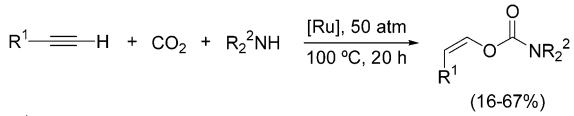
R^1 = Bu^n, Bu^t, Ph
R^2 = Me, Et, Pr^i, Bu^t, Cy, Bn, adamant-1-yl, *n*-$C_{17}H_{35}$, Bz, PhCHOH, $MeCO(CH_2)_2$, MeCONHCHMe

Scheme 209



R^1 = H, Me, $Pent^n$
R^2 = Me, Et

Scheme 210



R^1 = Bu^n, Ph
R^2 = Me, Et
R^2-R^2 = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$

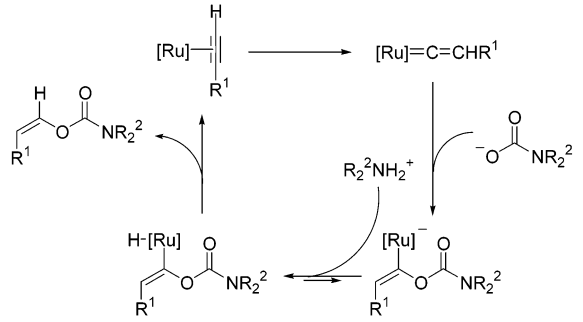
Many other structurally different carboxylic acids and alkynes were subjected successfully to the above-mentioned reaction conditions.[272]

This catalytic system also allowed the addition of acetic acid to propargyl carbonates, leading to the corresponding 2-acetoxyallyl carbonates in 40−63% yield and with very high regioselectivity (Scheme 209).[273] The products obtained were utilized as appropriate substrates in the palladium-catalyzed allylation of carbonucleophiles.

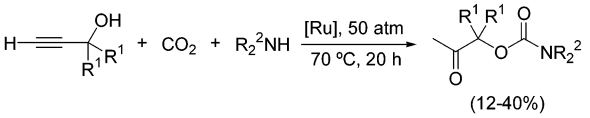
On the other hand, the ruthenium-catalyzed addition of carboxylic acids to alkynes has been better understood due to the deep studies and outstanding contributions by the group of Dixneuf. The early work focused on the ruthenium-catalyzed synthesis of vinyl carbamates from terminal alkynes, carbon dioxide, and diethylamine.[274] The reaction was performed under 50 atm CO_2 at 140 °C for 20 h using $Ru_3(CO)_{12}$ as catalyst. However, the reaction exhibited low selectivity, giving mixtures of regio- and stereoisomers.

Better behavior was observed for mononuclear ruthenium catalysts such as $RuCl_3 \cdot xH_2O$, $[(p\text{-cymene})RuCl_2]_2$, $(p\text{-cymene})Ru(PMe_3)Cl_2$, $(C_6Me_6)Ru(PMe_3)Cl_2$, or $(NBD)Ru(Py)_2Cl_2$. Both the yield and selectivity were notably improved, the carbamate adding exclusively to the terminal carbon of the alkyne with major *Z* stereochemistry (Scheme 210).[275] It is noteworthy that this catalytic formation of vinyl carbamates is restricted to secondary alkylamines, no addition being observed for primary amines. The fact that only terminal but not internal alkynes react, together with the regioselectivity of the reaction, led the authors to propose a mechanism involving ruthenium−vinylidene species.[61,175] Thus, rearrangement of the η^2-alkyne−metal complex to a η^1-vinylidene−metal intermediate followed by addition of the carbamate to the more electrophilic carbon atom, pro-

Scheme 211

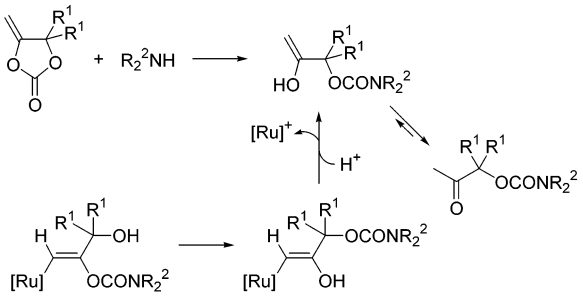


Scheme 212



R^1 = H, Me
R^2 = Et
R^2-R^2 = $(CH_2)_4$, $(CH_2)_5$

Scheme 213

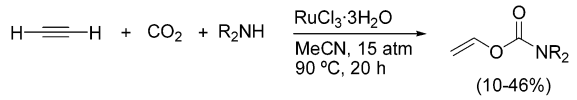


tonation at the metal center, and final reductive elimination would account for the formation of the vinylcarbamate (Scheme 211). Though no comment is made regarding the stereoselectivity of the reaction, the *Z* stereochemistry may be preferred in order to minimize the steric repulsion between the R^1 group and the bulkier ruthenium atom. Similar results were obtained by Mitsudo and Watanabe but using $Ru(\eta^5\text{-cod})_2-R_3P$ and $Ru(COD)(COT)-R_3P$ as catalytic systems.[276]

In contrast, when a propargyl alcohol was used as substrate in the presence of $[(NBD)RuCl_2]_n$ as catalyst, addition of the carbamate occurred at the substituted carbon atom of the triple bond, affording *O*-*β*-oxopropyl-*N*,*N*-dialkylcarbamates in low to moderate yields (Scheme 212).[277] The presence of the hydroxy group seemed to play an important role in driving the regioselective attack of the carbamate, since low regioselectivity was observed starting from the corresponding propargylic methyl ether. Two likely pathways were suggested to rationalize the formation of the products: (a) addition of the secondary amine to the carbonyl carbon of a cyclic carbonate or (b) insertion of the propargyl alcohol in the (carbamate)O−Ru bond, followed by intramolecular transesterification (Scheme 213).

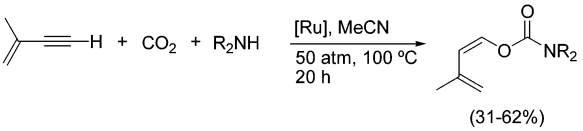
Acetylene itself was found to react with CO_2 and secondary amines in the presence of $RuCl_3 \cdot 3H_2O$ to give the corresponding vinyl carbamates in one step, though in low to moderate yields (Scheme 214).[278]

Scheme 214



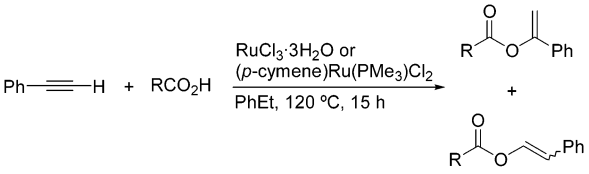
R = Et
R-R = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$

Scheme 215



R = Et
R-R = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$
[Ru] = $(dppe)Ru[\eta^3\text{-}CH_2{=}C(Me)CH_2]_2$

Scheme 216



R = Me, Ph, Ph(Et)CH, 2-thienyl, MeCH=CH

Those secondary amines of low steric hindrance and high basicity seemed to be the most favorable for the formation of the carbamates.

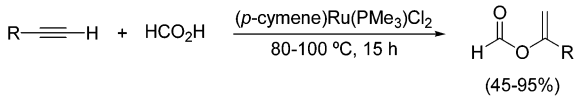
The carbamate synthesis methodology was also applied to the enyne isopropenylacetylene as starting material. However, the previously described catalysts of the type $(arene)Ru(PR_3)Cl_2$ failed in this reaction. Instead, ruthenium(II) catalyst precursors of the type $[Ph_2P(CH_2)_nPPh_2]Ru[\eta^3\text{-}CH_2{=}C(Me)CH_2]_2$, containing a hydrocarbon-based chelating bidentate phosphine ligand, were effective in this process, giving rise to *O*-1-(1,3-dienyl) carbamates in a regio- and stereoselective manner (Scheme 215).[279] The catalytic activity of the ruthenium complex showed a strong dependence on the chelating ligand, the complex with $n = 2$ being the most active. The same regiochemistry mentioned above was exclusively observed, whereas *Z* stereochemistry was predominantly produced in 75−80% selectivity.

Mononuclear ruthenium compounds such as $RuCl_3 \cdot 3H_2O$ and $(p\text{-cymene})Ru(PMe_3)Cl_2$, which were efficient catalysts in the synthesis of vinyl carbamates, also catalyzed the addition of carboxylic acids to phenylacetylene (Scheme 216).[280] Thus, saturated, α,*β*-unsaturated, and aromatic carboxylic acids were added to phenylacetylene, the regio- and stereochemistry of the corresponding enol esters depending on the acid, catalyst, and addition of a trialkylphosphine.

$RuCl_3 \cdot 3H_2O$ in the presence of 2 equiv of phosphine or $(arene)Ru(PMe_3)Cl_2$ complexes also catalyzed the regioselective Markovnikov addition of formic acid to terminal alkynes, giving the expected enol formates in 45−95% yield, which in addition were effective formylating agents (Scheme 217).[281]

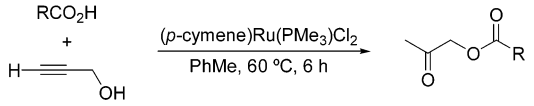
When propargyl alcohol was subjected to the ruthenium-catalyzed addition of different carboxylic acids, *β*-oxopropyl esters were formed in one step and in a similar way as that described for the addition of

Scheme 217



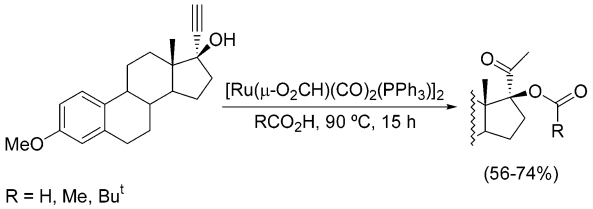
R = Me, Bu^n, Ph

Scheme 218



R = Ph, Ph(Et)CH, (*E*)-MeCH=CH, (*E*)-HO$_2$CCH=CH
RCO$_2$H = Cbz-L-Pro, Boc-L-Pro, Cbz-L-Gly, Cbz-L-Asp

Scheme 219



R = H, Me, Bu^t

carbamates (see Schemes 212 and 213).[277] The reaction could be extended to dicarboxylic acids and *N*-protected amino acids (Scheme 218)[282] as well as to other alkynols.[283]

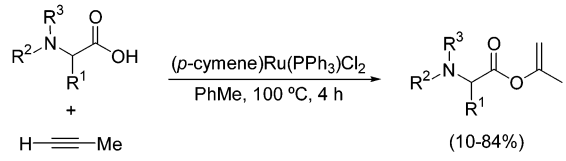
The above interesting reaction was applied to steroids containing both hydroxy and ethynyl groups at the 17-position, which by reaction with carboxylic acids were selectively transformed into β-oxopropyl esters with retention of the configuration. In this case, [Ru(μ-O$_2$CH)(CO)$_2$(PPh$_3$)]$_2$ complex had to be used instead of (*p*-cymene)Ru(PMe$_3$)Cl$_2$ in order to get good yields.[284] An example using mestranol as starting material is depicted in Scheme 219, the reaction proceeding also with good yields for norethindrone and levonorgestrel.

[Ru(μ-O$_2$CH)(CO)$_2$(PPh$_3$)]$_2$ also exhibited better behavior than other complexes in the catalytic addition of halogenated aromatic acids to alkynes.[285] Although this precursor catalyst promoted the addition of carboxylic acids to internal alkynes with low regioselectivity, the addition to a functionalized internal alkyne such as 3-hexyn-1-ol led regioselectively to a δ-ketoester under mild conditions.[286]

Amino acid derivatives have also been reported to add to alkynes under ruthenium catalysis, providing the corresponding enol esters. For instance, Dixneuf et al. described a general synthesis of isopropenyl amino esters by regioselective addition of *N*-protected amino acids to propyne, catalyzed by arene−ruthenium−phosphine complexes under relatively mild reaction conditions (100 °C, 2−3 bar, 4 h) (Scheme 220).[287] The reaction occurred without deprotection of the amino group and with no racemization, no addition being observed for unprotected amino acids. The resulting enol esters were successfully utilized as acylating agents in the preparation of amino amides, tertiary amides, and peptides.[288]

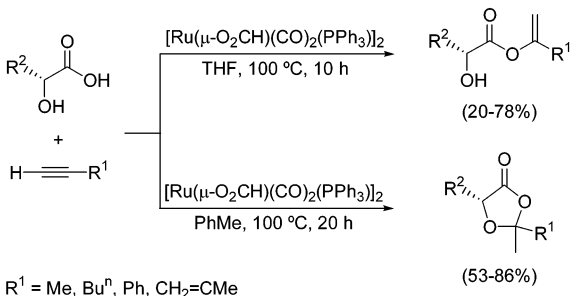
α-Hydroxy acids also could be added to terminal alkynes properly activated with [Ru(μ-O$_2$CH)(CO)$_2$-(PPh$_3$)]$_2$. When the reaction was performed in THF,

Scheme 220



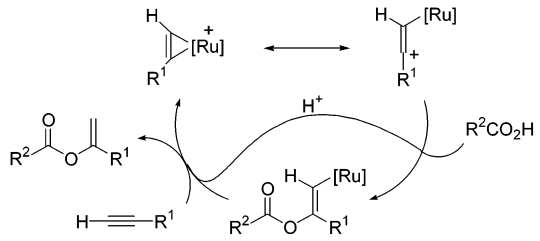
R^1 = H, Me, Bn, CH$_2$CO$_2$H
R^1-R^2 = (CH$_2$)$_3$
R^3 = H, Cbz, Boc

Scheme 221



R^1 = Me, Bu^n, Ph, CH$_2$=CMe
R^2 = Me, Ph

Scheme 222



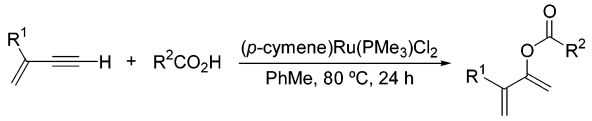
the corresponding enol esters were obtained in moderate to good yields and without racemization. However, with toluene as solvent, further activation of the carbon−carbon double bond in the intermediate enol ester afforded in a direct manner optically active 1,3-dioxolan-4-ones (Scheme 221).[289] This intramolecular cyclization was diastereoselective in favor of the *cis*-isomer (up to 95:5)

The following catalytic cycle was proposed by Dixneuf's group to explain the addition of carboxylic acids to terminal alkynes catalyzed by ruthenium complexes, including (a) electrophilic activation by ruthenium of the carbon−carbon triple bond, (b) nucleophilic *trans*-attack of the carboxylate to the substituted carbon, and (c) protonation of the resulting intermediate (Scheme 222).[268b]

(Arene)(phosphine)ruthenium(II) complexes were also very efficient catalysts in the regioselective addition of carboxylic acids and *N*-protected amino acids to butenyne derivatives, yielding in this case 2-acyloxy-1,3-dienes in good yields (Scheme 223).[290] It is worth noting that the regioselectivity was the opposite of that observed for the addition of carbamates to the same type of butenynes (see Scheme 215).[279]

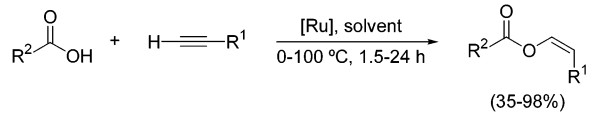
In the early 1990s, Dixneuf et al. introduced a bis-(2-methylpropenyl)ruthenium complex containing chelating 1,*n*-bis(diphenylphosphine)alkane ligands, [Ph$_2$P(CH$_2$)$_n$PPh$_2$]Ru[η^3-CH$_2$═C(Me)CH$_2$]$_2$, that completely reversed the previously observed regiochemistry for the addition of carboxylic acids to alkynes.[291]

Scheme 223

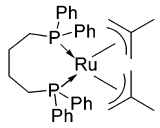


R^1 = H, Me
R^2 = Bu^t, (*E*)-MeCH=CH, Ph, 2,6-$F_2C_6H_3$

Scheme 224

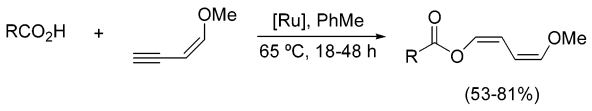


R^1 = Bu^n, Ph
R^2 = Me, Bu^n, $ClCH_2$, Cl_2CH, CF_3, $MeOCH_2$, Ar
CH_2=CH, allyl, (*E*)-MeCH=CH
R^2CO_2H = Boc-Ala, Boc-Phe, Cbz-Ala



[Ru] = (dppb)Ru[η^3-CH_2=C(Me)CH_2]$_2$

Scheme 225



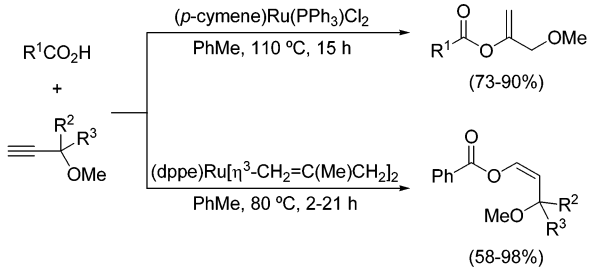
R = Me, Bu^n, $MeOCH_2$, CH_2=CMe, Bn, Ph, *p*-ClC_6H_4
[Ru] = (dppb)Ru[η^3-CH_2=C(Me)CH_2]$_2$

Moreover, the corresponding anti-Markovnikov (*Z*)-enol esters were obtained in a stereoselective manner as a result of direct *trans*-addition of the carboxylic acid to the terminal alkyne (Scheme 224). The best selectivity was observed for the catalyst precursor with the diphosphine ligand containing the longest chain (n = 4), except for the addition to the bulky HC≡CSiMe_3, where the ligand with n = 2 was superior. Thus, steric effects (also in the substrates) rather than electronic factors were invoked to account for the regio- and stereoselectivities observed. The reaction also worked very nicely for *N*-protected α-amino acids (75−97%) and for isopropenylacetylene (77−92%). It was also established that these complexes led to the in situ formation of the corresponding [$Ph_2P(CH_2)_nPPh_2$]Ru(η^2-O_2CR)$_2$ intermediates acting as catalyst precursors.

The above-described catalytic system was a very efficient catalyst precursor for the preparation of (*Z*)-dienyl esters from carboxylic acids and enynes.[292] The process took place under mild reaction conditions and with very high regio- and stereocontrol for the substrates 2-methylbut-1-en-3-yne and (*Z*)-1-methoxybut-1-en-3-yne, the latter providing the corresponding (*Z*,*Z*)-1,3-dienes (Scheme 225). Both the (*Z*)-enol esters and (*Z*)-dienyl esters obtained were successfully utilized for the stereoselective preparation of (*Z*)-enamines by reaction with secondary amines.[293]

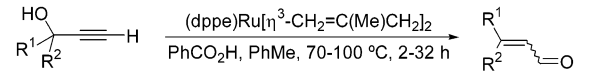
The important role of the nature of the ruthenium catalyst precursor in the alkyne activation was

Scheme 226



R^1 = Pr^i, Ph, $CbzNHCH_2$, $BocNHCHMe$; R^2 = R^3 = H
R^1= Ph; R^2= H, Me, Et; R^3 = Me, Et, Bu^n, Bu^i, $Pent^n$, Ph; R^2-R^3 = $(CH_2)_5$

Scheme 227



R^1 = Me, Ph
R^2 = Me, Ph, Bu^i, $(CH_2)_2CH=CH_2$, $(CH_2)_2CH=CMe_2$,

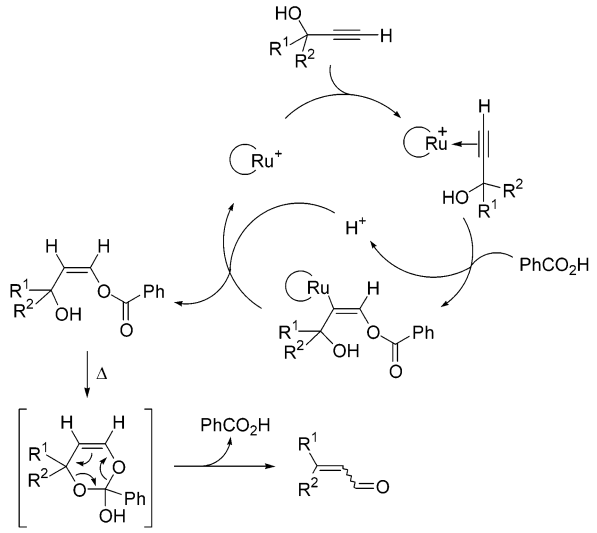
demonstrated in the elegant control of the regiochemistry of addition of carboxylic acids to propargyl ethers reported by Dixneuf et al.[294] Thus, in the presence of (*p*-cymene)Ru(PPh_3)Cl_2, several carboxylic acids added to methyl propargyl ether in a Markovnikov fashion to form the corresponding enol esters in high yields (73−90%) (Scheme 226). On the other hand, when (dppe)Ru[η^3-CH_2=C(Me)CH_2]$_2$ was utilized as a catalyst precursor, addition of benzoic acid to a variety of propargyl ethers led to (*Z*)-3-methoxyalk-1-en-1-yl benzoates in good to excellent yields (58−98%) as a result of a high stereo- and regioselective anti-Markovnikov mode of addition (Scheme 226).

(dppe)Ru[η^3-CH_2=C(Me)CH_2]$_2$ in the presence of benzoic acid was also an efficient catalyst precursor for the isomerization of prop-2-yn-1-ols to the corresponding enals (Scheme 227). Unfortunately, the process showed low diastereoselectivity, 1:2 mixtures of the (*Z*)- and (*E*)-diastereoisomers being obtained.[295] The key step of the process was the *trans*-anti-Markovnikov addition of benzoic acid to the activated alkyne. Protonolysis of the resulting intermediate would generate a (*Z*)-3-hydroxyprop-1-en-1-yl benzoate, which subjected to the thermal elimination of benzoic acid gave the mentioned α,β-enals (Scheme 228).

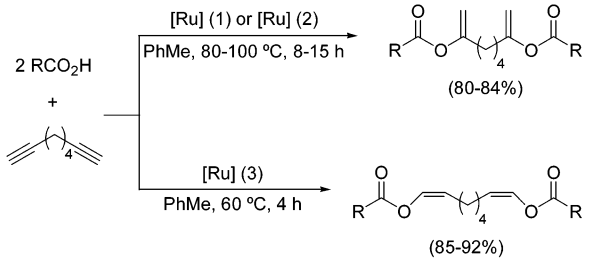
Activation of octa-1,7-diyne toward the regioselective Markovnikov addition of carboxylic acids was achieved with the binuclear complex [Ru(μ-O_2CH)-$(CO)_2(PPh_3)$]$_2$ and (*p*-cymene)Ru(PPh_3)Cl_2, the former being more efficient. However, in the presence of (dppb)Ru[η^3-CH_2=C(Me)CH_2]$_2$, containing a diphosphine chelating ligand, anti-Markovnikov addition furnished the corresponding (*Z*,*Z*)-dienol diesters in good yields (Scheme 229). Optically active dienol diesters were obtained in all cases from α-amino acids.[296]

Different behavior to that described up to this point was observed when two molecules of terminal alkynes were combined with one of carboxylic acid in the presence of Cp*Ru(COD)Cl, affording (1*E*,3*E*)-1,4-

Scheme 228

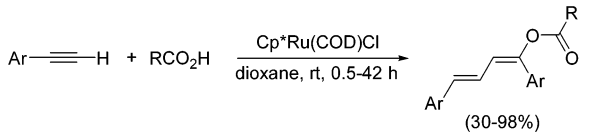


Scheme 229



R = H, Me, Ph, $CbzNHCH_2$, CbzNHCHMe, BocNHCHMe
[Ru] (1) = $[Ru(\mu\text{-}O_2CH)(CO)_2(PPh_3)]_2$
[Ru] (2) = (*p*-cymene)$Ru(PPh_3)Cl_2$
[Ru] (3) = (dppb)Ru[η^3-CH_2=C(Me)CH_2]$_2$,

Scheme 230

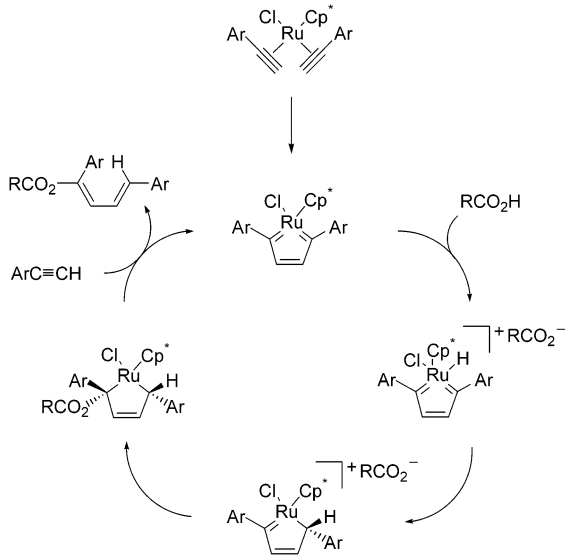


Ar = Ph, *p*-$MeOC_6H_4$, *p*-NCC_6H_4
R = H, Bu^t, Ph, $CHCl_2$, CH_2CN, CH_2OMe

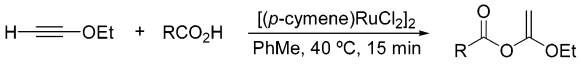
disubstituted-1-acyloxybuta-1,3-dienes (Scheme 230).[297] The products were obtained as a result of a highly regioselective head-to-head coupling of terminal alkynes with stereoselective 1,4-addition of the proton and the carboxylate. The efficiency of the reaction was shown to depend strongly on both the nature of the solvent and the acid, as the weaker the acid the better the yield obtained. It was suggested that a metallacycle bis-carbene ruthenium structure could be involved in the catalytic cycle, which by protonation followed by carboxylate addition would generate the mentioned (1*E*,3*E*)-dienes (Scheme 231).

Kita et al. discovered that complexes of the type (arene)$Ru(PR_3)Cl_2$, which gave good results for the formation of enol esters, were inadequate for the case of 1-ethoxyvinyl esters. Instead, this group utilized [(*p*-cymene)$RuCl_2]_2$ as efficient catalyst precursor for the addition of different carboxylic acids to ethoxyacetylene (Scheme 232).[298] The reaction was shown to be fast and to proceed in high yields under mild conditions, the 1-ethoxyvinyl esters obtained being

Scheme 231

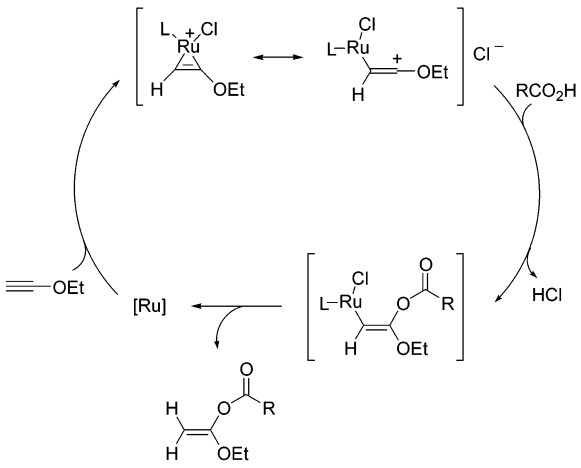


Scheme 232



R = Me, Bu^t, Ph, $MeOCO(CH_2)_n$, $PhOCO(CH_2)_n$, $TMSEOCO(CH_2)_n$
n = 2, 5

Scheme 233

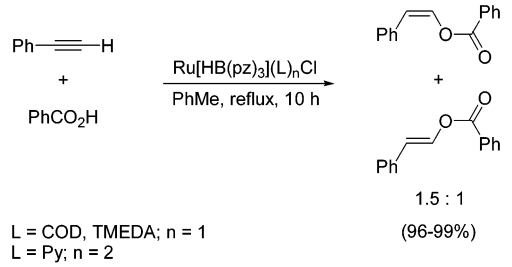


used in the acylation of amines and alcohols. A catalytic cycle was proposed in which the regiochemistry of the reaction was explained by the nucleophilic attack of the carboxylic acid to the most stabilized vinylic carbenium ion in the activated alkyne (Scheme 233).

Ruthenium dicarbonyl acetate, in the presence of a phosphine ligand (e.g., Bu_3P) and a selectivity enhancer (e.g., THF, CO, MeCN, etc.), was an adequate catalytic system for the high-yielding and selective preparation of vinyl esters (e.g., vinyl pivalate) from alkynes (e.g., acetylene) and carboxylic acids (e.g., pivalic acid).[299]

Ruthenium complexes containing the tris(pyrazolyl)borate ligand $[HB(pz)_3]$[189] found application not only in the intermolecular addition of allyl alcohols to acetylenes (see Scheme 127) but also in the addition of benzoic acid to phenylacetylene (Scheme

Scheme 234



Scheme 235

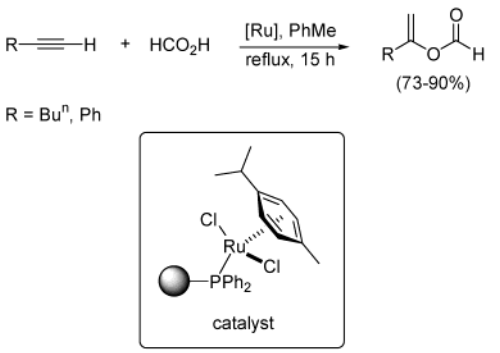
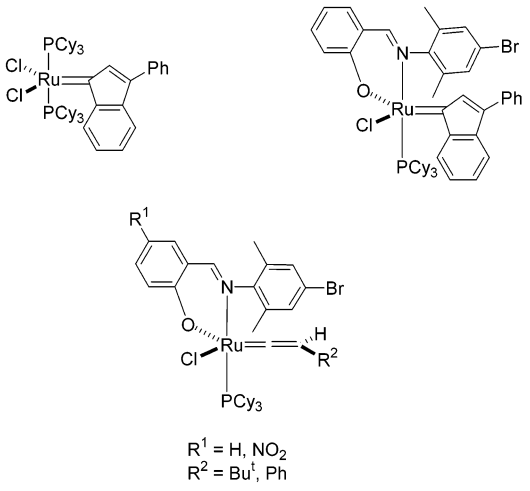


Chart 4



234).[188] The specific anti-Markovnikov mode of addition seems to be in agreement with the participation of ruthenium vinylidene species, though the stereoselectivity was rather low and slightly in favor of the (*E*)-stereoisomer (1.22−1.63:1).

Leadbeater et al. prepared a polymer-supported arene ruthenium complex by thermolysis of the dimer [(*p*-cymene)$RuCl_2$]$_2$ with polymer-supported triphenylphosphine, which was shown to catalyze the addition of formic acid to terminal alkynes and diynes (Scheme 235).[300] The yields of the enol formates were comparable to those obtained under homogeneous catalysis, and the catalyst could be recycled and used five times without any apparent loss of activity.

More recently, Verpoort et al. synthesized and tested a series of ruthenium catalysts for the nucleophilic addition of carboxylic acids to terminal alkynes (Chart 4). Depending on the catalytic system, substrate, and carboxylic acid, the reaction could be relatively driven toward the formation of alk-1-en-

Scheme 236

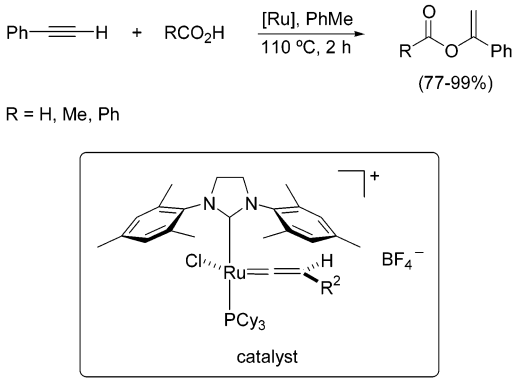
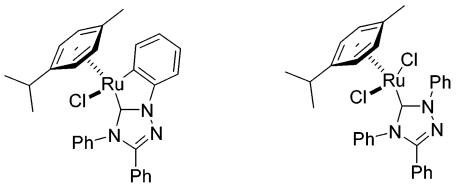


Chart 5



2-yl esters, alk-1-en-1-yl esters, or enyne dimerization products. In general, the Markovnikov products were the major ones, though the regioselectivity was low with only a few exceptions, such as in the addition of formic acid to phenylacetylene.[301]

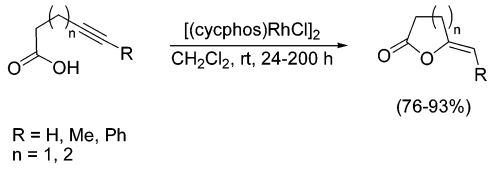
The regioselectivity could be improved by developing a new ruthenium catalyst belonging to the vinylidene series and bearing a 4,5-dihydroimidazol-2-ylidene moiety, which showed a notable preference toward the formation of the Markovnikov enol esters, especially in the carboxylic acid addition to phenylacetylene (Scheme 236).[302]

Catalysts of the type (*p*-cymene)Ru(triazol-5-ylidene)Cl_n could complement the above-mentioned results to provide mainly the anti-Markovnikov products, the (*Z*)- and (*E*)-diastereoselectivity depending on the catalyst and substrate used (Chart 5).[303]

4.2. Rhodium Catalysts

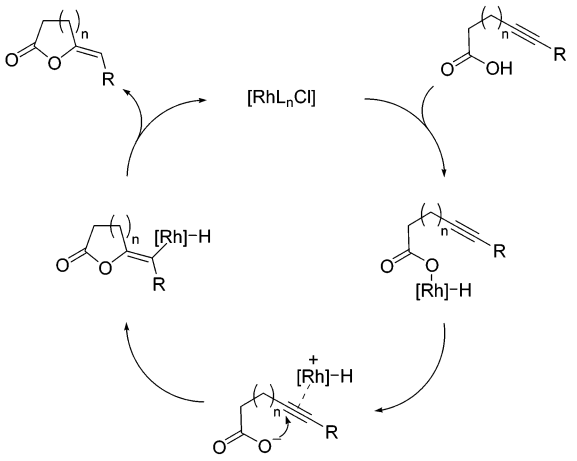
To the best of our knowledge, Chan, Marder et al. are the only ones who used rhodium complexes to catalyze the addition of carboxylic acids to alkynes and applied more specifically to the cyclization of alkynoic acids to alkylidene lactones.[304] Thus, high-yield lactonizations were accomplished in the presence of the rhodium(I) complex [(cycphos)RhCl]$_2$ [cycphos = 1,2-bis(dicyclohexylphosphino)ethane] at room temperature in dichloromethane (Scheme 237).

Scheme 237



The catalyst showed superior catalytic activity when compared to other transition-metal complexes [e.g., $Pd(PPh_3)_4$] or mercuric salts. In addition, exclusive

Scheme 238



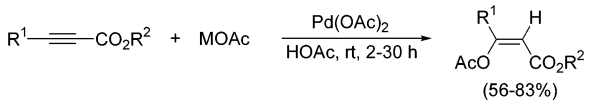
Z stereochemistry was observed in the products as a result of the *trans*-addition of the carboxylate across the carbon−carbon triple bond, formation of five- versus six-membered rings also being favored. The corresponding 14-electron monomer complex was suggested as responsible for the catalytic activity, taking part in a catalytic cycle involving hydroxy group activation, nucleophilic attack of the carboxylate on the coordinated alkyne, and reductive elimination (Scheme 238).

4.3. Palladium Catalysts

Palladium catalysts are the ideal complement to ruthenium catalysts for the addition of carboxylic acids to alkynes, since the latter are exclusively used in intermolecular processes whereas the former have been mainly applied in intramolecular reactions.[174] The palladium-catalyzed intermolecular addition of carboxylic acids to alkynes is restricted to very few examples. Thus, Lu et al. described in the early 1990s the regio- and stereospecific hydroacetoxylation of 2-alkynoic acid derivatives with lithium acetate in acetic acid in the presence of palladium acetate at room temperature (Scheme 239).[305] The corresponding (*Z*)-enol esters were obtained as a result of the *trans*-attack of the acetate anion at the coordinated carbon−carbon triple bond, followed by protonolysis.

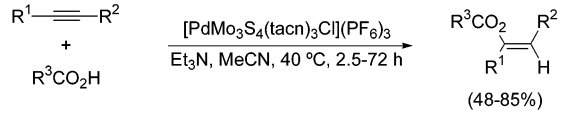
The polynuclear transition-metal−sulfur complexes of the type $[PdMo_3S_4(tacn)_3Cl](PF_6)_3$,[203] mentioned in the hydroalkoxylation section, were also found to catalyze the regio- and stereoselective addition of carboxylic acids to electron-deficient alkynes (Scheme 139).[306] Both terminal and internal alkynes were subjected to this catalytic system, giving rise to the corresponding (*Z*)-vinyl esters in moderate to good yields (Scheme 240). A similar mechanism to that described in Scheme 140 was suggested.

Scheme 239



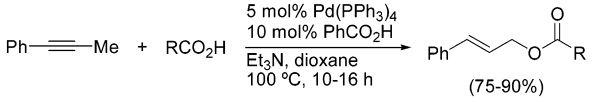
R^1 = Me, Bu^n, Ph
R^2 = OMe, OBn, $OCH_2CH{=}CHCH_2OH$, NH_2
M = Li, Na

Scheme 240



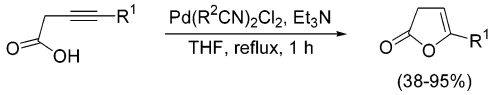
R^1 = H, Me, CO_2Me
R^2 = CO_2Me, CO_2Et, CO_2Bu^t, COPh, SO_2Tol
R^3 = Me, Et, Ph, $CH_2{=}C(Me)$, PhCH=CH, *m*-ClC_6H_4, 2-furyl, $Bu^tOCONHCH_2$

Scheme 241



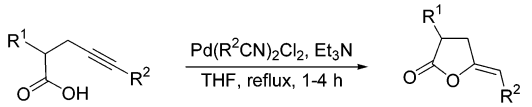
R = Me, Pr^i, Bu^t, Ph

Scheme 242



R^1 = Me, Hex^n, Oct^n, Ph
R^2 = Me, Ph

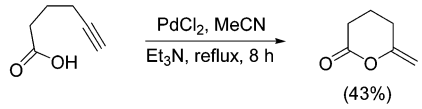
Scheme 243



Z/*E* 84:16-100:0

R^1 = H, Me, Bu^n, Hex^n, Ph, Bn, TMS
R^2 = Me, Ph

Scheme 244



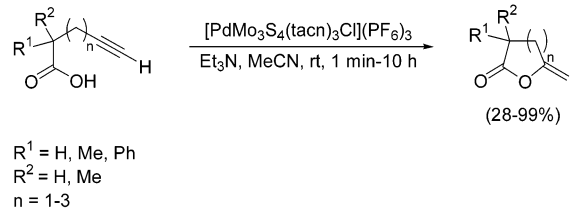
On the basis of Yamamoto's methodology,[70] Zhang et al. reported the effective addition of carboxylic acids to 1-phenylprop-1-yne to give the corresponding allylic esters in good isolated yields (Scheme 241).[201]

The palladium-catalyzed intramolecular addition of carboxylic acids to alkynes is a versatile tool for the direct construction of lactone rings of different size and substitution.[69f,173] The pioneering work by Utimoto et al. revealed the regioselective 5-*endo*-*dig* cyclization of 3-alkynoic acids under the action of palladium(II) and in the presence of triethylamine to afford 3-alken-4-olides in moderate to excellent yields (Scheme 242).[307]

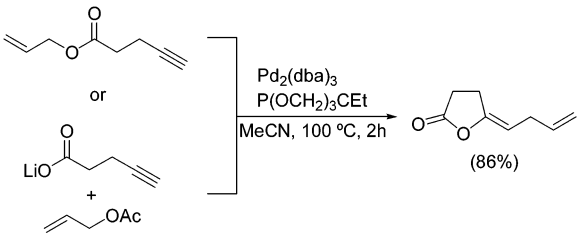
Under the above-mentioned reaction conditions, 4-pentynoic acids bearing an alkyl group at the 2-position were exclusively cyclized in a 5-*exo*-*dig* manner to furnish mainly the corresponding (*Z*)-4-penten-4-olides (Scheme 243). On the other hand, cyclization of 5-hexynoic acid took place in a 6-*exo*-*dig* fashion to give an exocyclic 5-hexen-5-olide (Scheme 244).[307]

A more recent highly effective catalytic system was developed by Hidai et al. for the cyclization of 3-, 4-, and 5-alkynoic acids to the corresponding enol lactones under very mild reaction conditions. This

Scheme 245



Scheme 246

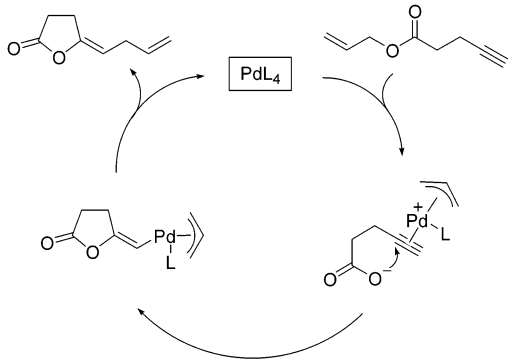


system was composed of the mixed-metal sulfide cluster with a cuboidal core $[PdMo_3S_4(tacn)_3Cl](PF_6)_3$,[203] (see Schemes 139 and 240 for other catalytic applications of this complex in this review) and a small amount of triethylamine in acetonitrile. 5-Alkynoic acids gave the corresponding δ-lactones, whereas 3- and 4-alkynoic acids led to the corresponding γ-lactones, the formation of the latter proceeding much faster than that of the former (Scheme 245).[308] However, the cyclization of 6-heptynoic acid to the corresponding ϵ-lactone was slow and low-yielding. A similar mechanism to that described in Scheme 140 was suggested.

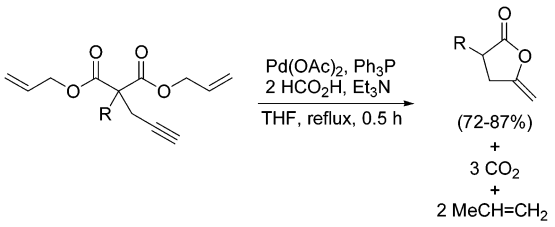
Alternatively, the intermediate alkenylpalladium species could be easily generated by the intramolecular palladium(II)-catalyzed cyclization of lithium alkynoates and coupled with different allyl halides providing allyl-substituted butenolides stereoselectively.[309] A different approach to the synthesis of unsaturated lactones was introduced by Tsuda et al. based on the use of allylic alkynoates or a related system of lithium alkynoates and allylic acetates.[310] In both cases, the regio- and stereoselective cyclization of the alkynoate moiety produced the corresponding γ-(*E*)-alkylidene-γ-butyrolactones, the best results being obtained with trimethylolpropane phosphite as ligand (Scheme 246). A reasonable reaction pathway was suggested involving oxidative addition of the Pd(0) complex to the allylic alkynoate, followed by the *trans*-nucleophilic attack on the carbon−carbon triple bond activated by the (π-allyl)palladium cation, and final coupling of the π-allyl and alkenyl moieties with regeneration of the Pd(0) complex (Scheme 247).

Different behavior was observed when the allylic alkynoate moiety was present in a diallyl alkyl(2-propynyl)malonate and subjected to palladium(0)-catalyzed cyclization and hydrogenolysis with formic acid.[311] In this case, the corresponding α-alkyl-γ-methylidene-γ-lactones were rapidly obtained in good yields and under very mild conditions (Scheme 248). On the basis of experimental results, a reaction mechanism was proposed in which a (π-allyl)palladium malonate intermediate is first generated, which suffers assisted cyclization to form an alkenyl-(π-allyl)palladium lactone. Removal of the (π-allyl)-palladium carboxylate moiety by hydrogenolysis with triethylammonium formate and decarboxylation and hydrogenolysis of the (π-allyl)alkenylpalladium with formate would give the expected lactones (Scheme 249).

Scheme 247

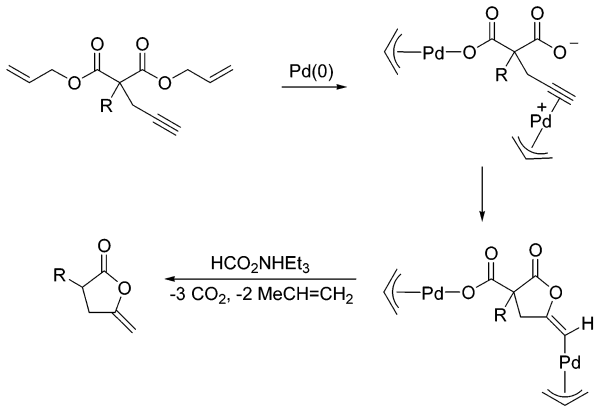


Scheme 248



R = Hex^n, Bn, $CH_2C{\equiv}CH$, $TBDMSO(CH_2)_4$, $MeC(OCH_2CH_2O)(CH_2)_3$, geranyl

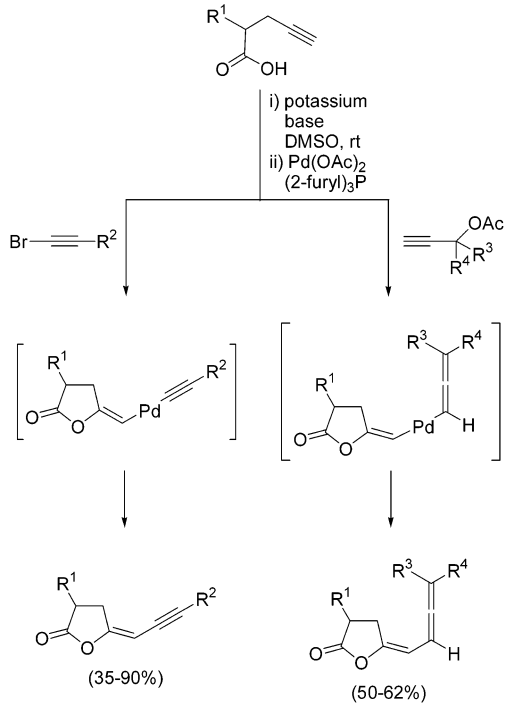
Scheme 249



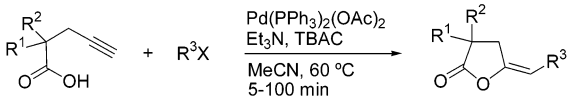
Balme et al. synthesized a series of biologically active ynenol-[312] and allenenollactones[313] in a stereoselective manner and in high yields by reacting γ-acetylenic carboxylates with 1-bromo-1-alkynes and propargyl acetates, respectively, under palladium catalysis (Scheme 250). In these reactions, only the potassium carboxylate was shown to be effective in the cyclization, which could be better promoted in the presence of tri(2-furyl)phosphine as the ligand. The reactions were suggested to take place by nucleophilic attack of the carboxylate anion on the activated alkyne by a σ-ethynyl- and σ-allenylpalladium intermediate, respectively, followed by reductive elimination.

Cacchi et al. reported the palladium-catalyzed reaction of vinyl triflates and vinyl (or aryl) halides

Scheme 250



Scheme 251



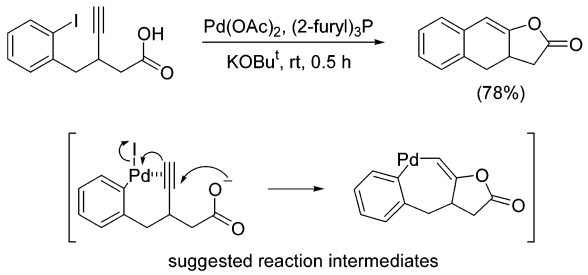
R^1 = H, CO_2Me
R^2 = alkyl, CO_2Me
R^3 = vinyl, aryl
X = TfO, Br, I

with 4-pentynoic acid, 2,2-disubstituted 4-pentynoic acids, and 5-susbtituted 4-pentynoic acids, which led to the corresponding (*E*)-*δ*-vinyl(or aryl)-*γ*-methylidene-*γ*-butyrolactones in good to high yields and in a regio- and stereoselective manner (Scheme 251).[314] The reactions were performed with catalytic amounts of $Pd(PPh_3)_2(OAc)_2$ or $Pd(PPh_3)_4$, Et_3N, and TBAC, the presence of chloride anions being crucial for the reaction to occur. The general mechanism involving intramolecular nucleophilic attack of the carboxylate anion on the palladium(II)-activated alkyne and subsequent reductive elimination was proposed to explain the formation of the exocyclic enol lactones.

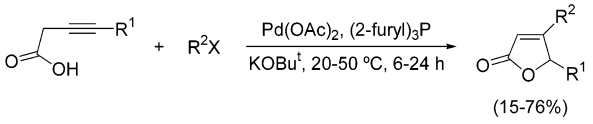
On the basis of the above-described approach, Balme et al. developed a novel tandem carbopalladation−heterocyclization process starting from pentynoic acids 3- or 5-substituted with an iodoaryl moiety.[315] The corresponding benzoannulated enol lactones were obtained in good yields (Scheme 252), this methodology being applied to the formal synthesis of the anti-ulcer agent U-68,215.

Under similar reaction conditions, 3-ynoic acids reacted with aryl, alkenyl, and 1-alkynyl halides to form 4,5-disubstituted 5*H*-furan-2-ones (Scheme 253).[316] The yields were rather low for alkenyl or 1-alkynyl bromides as well as for 4-phenyl-3-butynoic acid, and 4-substituted 5*H*-furan-2-ones could not be

Scheme 252

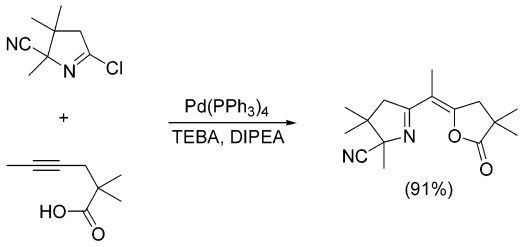


Scheme 253



R^1 = H, Me, Pr^n, Ph
R^2 = Ph, 2,4-$Cl_2C_6H_3$, CH_2=C(Me), $Pent^n$C≡C, 2-thienyl
X = Br, I

Scheme 254

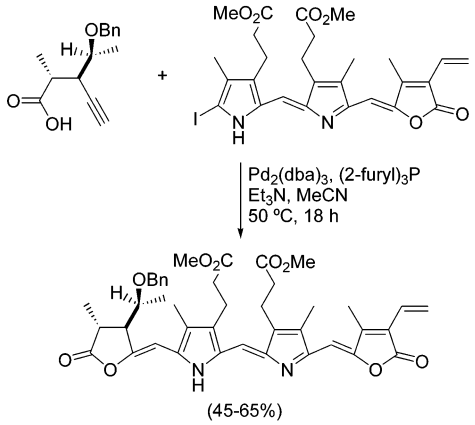


prepared from 3-butynoic acid. All products were obtained as a result of a base-catalyzed isomerization of the 3*H*-furan-2-ones first generated.

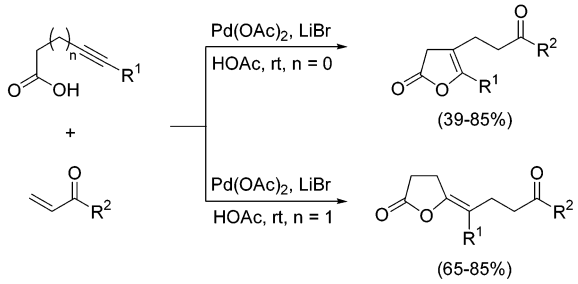
Jacobi et al. extended their strategy of the palladium(0)-initiated coupling−cyclization of triflates and alkynylamines[88] to alkynyl carboxylic acids as a key step in the synthesis of semicorrins.[317] For instance, the palladium-mediated coupling of an iminoyl chloride with a 4-hexynoic acid derivative afforded the corresponding enol−lactone as a 1:1 mixture of diastereomers (Scheme 254). The presence of the quaternary ammonium chloride was shown to be essential in order to get good results. A reaction mechanism similar to that depicted in Scheme 65 was presented to rationalize the formation of the products.[89] When a chiral 4-pentynoic acid and a 2-iodopyrrol derivative were subjected to the palladium-catalyzed coupling−cyclization protocol, the corresponding (*Z*)-bis-lactone was obtained stereoselectively (Scheme 255).[318]

The intermediate alkenylpalladium species resulting from the palladium-catalyzed intramolecular cyclization of alkynoic acids were also trapped with α,*β*-unsaturated carbonyl compounds. Thus, Lu et al. examined the oxypalladation−coupling reaction of alkynoic acids with α,*β*-unsaturated carbonyl compounds to give the corresponding lactones.[319] A variety of 3-butenolides and *γ*-alkylidene-*γ*-butyrolactones were obtained from 3- and 4-alkynoic acids, according to 5-*endo*-*dig* and 5-*exo*-*dig* modes of cyclization, respectively, the butyrolactones being formed stereoselectively, conforming to the *trans*-oxypalladation of the carbon−carbon triple bond (Scheme 256).

Scheme 255

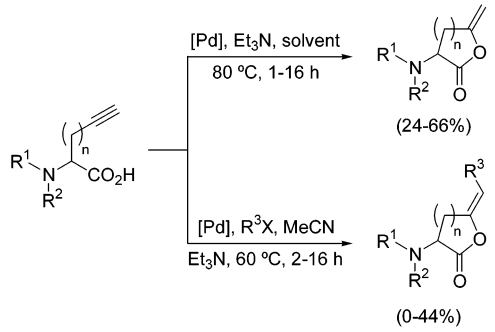


Scheme 256



R^1 = Pr^n, Bu^n, Ph; R^2 = H; n = 0
R^1 = H, Ph; R^2 = H, Me; n = 1

Scheme 257

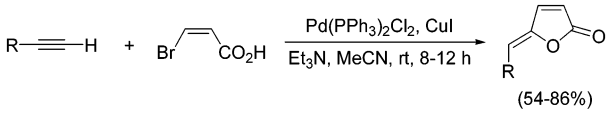


R^1, R^2 = protecting groups
R^3 = aryl, vinyl
n = 1, 2
X = I, OTf

More recently, as already pointed out in this review, Rutjes et al. employed enantiomerically pure acetylene-containing α-amino acids as versatile starting materials to accomplish the synthesis of various heterocycles under palladium catalysis (see Scheme 56).[81] Thus, the palladium-catalyzed cyclization of a variety of enantiopure *N*-protected amino acids furnished the corresponding five- and six-membered α-amino-γ-methylidene lactones, the latter being obtained in lower yields (Scheme 257). Unfortunately, when the reaction was performed in the presence of an aryl iodide or vinyl triflate, the expected cross-coupled products were isolated with complete racemization and low yields.

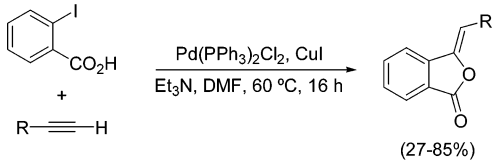
γ-Alkylidenebutenolides represent a wide variety of natural products, many of them displaying a wide range of biological activities. In particular, the (*Z*)-isomers are by far the most abundant, and therefore, there is great interest in their regio- and stereoselective synthesis.[320] The lactonization reaction, based on the catalytic oxypalladation of alkynoic acids, proved to be an adequate method to accomplish the synthesis of this type of compounds in a straightforward manner.

Scheme 258



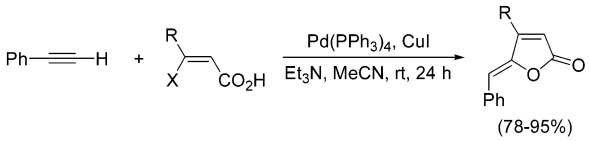
R = Ph, $Pent^n$, Hep^nCHOH, PhCHOH, $THPOCH_2$, Me_2COH, $MeOCH_2$, $HC{\equiv}CH_2OCH_2$

Scheme 259



R = H, CH_2OH, CMe_2OH, MeCH=CHCHOH, PhCHOH, *o*-C_6H_4CHOH, Ph, *m*-ClC_6H_4, 1-naphthyl, CO_2Me, 2,4-dimethoxy-5-pyrimidinyl

Scheme 260



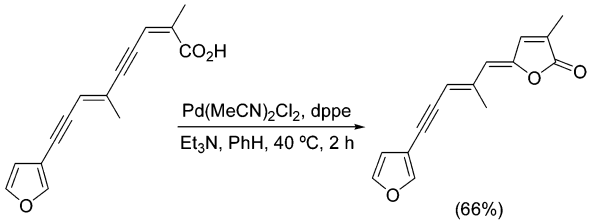
R = H, Ph
X = Br, I

For instance, Lu et al. reported a convenient approach to this type of compounds starting from (*Z*)-3-bromopropenoic acid and terminal alkynes through a tandem coupling−oxypalladation process under essentially the conditions of the Sonogashira coupling.[321] The *Z* stereoselectivity of the reaction was also explained in terms of the *trans*-addition of the carboxylate anion to the carbon−carbon triple bond (Scheme 258). This methodology found application in the total synthesis of both enantiomers of melodorinol.[322]

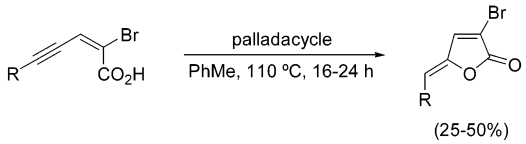
Parallel to this work, Kundu et al. discovered a stereoselective heteroannulation process by reacting *o*-iodobenzoic acid with various alkynes under palladium catalysis, leading to the (*Z*)-3-alkylidene phthalides as major compounds (Scheme 259).[323a] The corresponding isocoumarins were obtained in some cases as byproducts as a result of a 6-*endo-dig* cyclization reaction. In contrast to the $Pd(PPh_3)_2Cl_2$−CuI−Et_3N catalytic system, $Pd(PPh_3)_4$−$ZnCl_2$−Et_3N favored the formation of the isocoumarins in moderate to excellent yields.[323b]

Negishi et al. found that better yields and selectivities were obtained when $Pd(PPh_3)_4$ was used instead of $Pd(PPh_3)_2Cl_2$ in the cross-coupling lactonization tandem reaction between phenylacetylene and (*Z*)-β-halocinnamic or (*Z*)-β-haloacrylic acids (Scheme 260).[324] In all cases the *Z*/*E* ratio was higher than 30:1, the formation of the corresponding pyranones being minimized. This methodology was applied to the synthesis of the diacetate of rubrolide A,[324] (+)-goniobutenolide A,[325] and xerulin.[326]

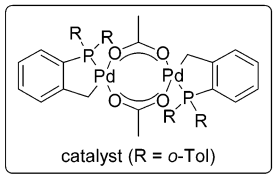
Scheme 261



Scheme 262



R = Bu^n, Ph, *p*-MeC$_6$H$_4$



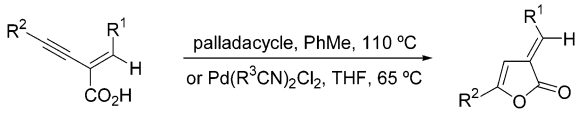
On the other hand, a slight variation on the above-described reaction conditions had to be introduced by Katsumura et al. for the successful lactonization of a freelingyne precursor. The reaction had to be performed in benzene at 40 °C and in the presence of dppe in order to prevent the formation of the stereoisomeric freelingyne (Scheme 261).[327]

The palladium complex described by Herrmann et al., *trans*-di(*μ*-acetato)-bis[(di-*o*-tolylphosphino)benzyl]dipalladium,[328] was successfully used by Rossi et al. to convert various easily available (*E*)-4-(1-alkynyl)-2-bromopropenoic acids into (*Z*)-3-bromo-5-ylidene-5*H*-furan-2-ones by heating the toluene solutions under argon at 110 °C for 16−24 h (Scheme 262).[329a] The (*Z*)-alkylidenebutenolides obtained were able to undergo palladium-catalyzed cross-coupling reactions with organozinc and organotin reagents. On the other hand, when (*Z*)-2-en-4-ynoic acids were reacted with heteroaryl halides in acetonitrile at 70−85 °C in the presence of K_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$, mixtures of 6-substituted 5-aryl-2*H*-pyran-2-ones and stereodefined 5-[(1,1-unsymmetrically disubstituted)methylidene]furan-2(5*H*)-ones were obtained as the major cyclization−coupling products.[329b] Fortunately, these compounds could be easily separated by chromatography.

The above shown palladacycle exhibited comparable or better behavior than $Pd(MeCN)_2Cl_2$ and $Pd(PhCN)_2Cl_2$ in the stereocontrolled synthesis of 5-aryl- and 5 alkyl-substituted (*E*)-3-[1-(aryl)methylidene]- and (*E*)-3-(1-alkylidene)-3*H*-furan-2-ones by cyclization of the corresponding (*E*)-2-(1-alkynyl)-3-aryl(or alkyl)propenoic acids (Scheme 263).[330]

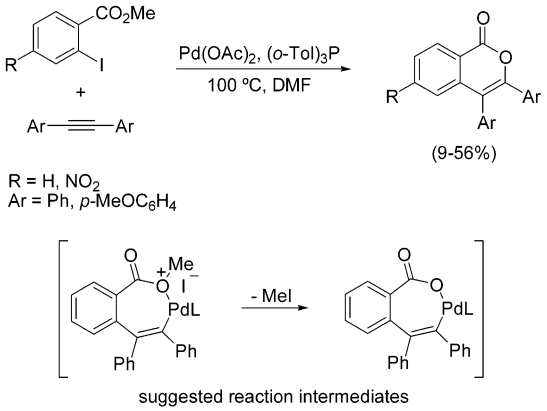
In the late 1980s, Heck et al. demonstrated that *o*-iodobenzoates reacted with internal acetylenes in the presence of palladium(II) acetate and a phosphine to give the corresponding isocoumarins in low to moderate yields (Scheme 264).[331] Primarily, diarylacetylenes were studied, 1-phenyl-1-hexyne giving a

Scheme 263



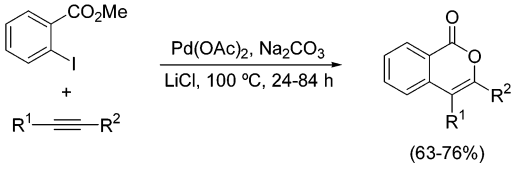
R^1 = Ph, *p*-FC$_6$H$_4$, 3,5-Cl$_2$C$_6$H$_3$, 3,4-(OCH$_2$O)C$_6$H$_3$, 2-thienyl
R^2 = Pr^n, Bu^n, Hex^n, Ph, *p*-MeC$_6$H$_4$
R^3 = Me, Ph

Scheme 264



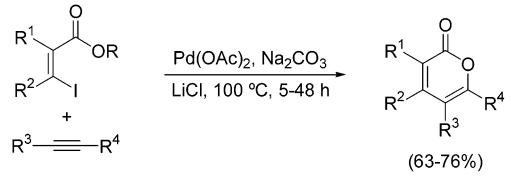
R = H, NO$_2$
Ar = Ph, *p*-MeOC$_6$H$_4$

Scheme 265



R^1 = Me, Et, Ph
R^2 = Bu^t, TMS, TIPS, 1-hydroxycyclohexyl

Scheme 266



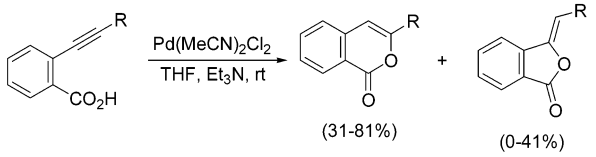
R^1 = Me, Et, Ph
R^2 = H, Me, Ph
R^1-R^2 = (CH$_2$)$_n$; n = 3-5
R^3 = Me, Ph, CMe$_2$OH, CO$_2$Et
R^4 = Bu^t, Ph, CMe$_2$OH, TES, TIPS

ca. 1:1 mixture of regioisomers. The reaction was proposed to proceed via a seven-membered ring palladacycle.

Better yields of isocoumarins were achieved by Larock et al. from methyl *o*-iodobenzoate and hindered alkyl-, silyl-, or aryl-substituted internal alkynes with the $Pd(OAc)_2-LiCl-Na_2CO_3$ system (Scheme 265).[146] The regiochemistry of the process arises from the addition of the aryl group to the less hindered carbon atom of the alkyne.

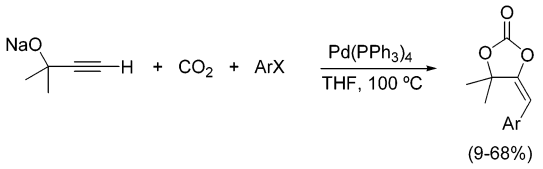
This protocol was extended to the preparation of 3,5,6-tri- and 3,4,5,6-tetrasubstituted 2*H*-pyran-2-ones by the reaction of vinylic iodides, bromides, or triflates bearing an ester functionality with internal alkynes (Scheme 266).[332] In general, good yields were obtained for both acyclic and cyclic esters and a

Scheme 267



R = Me, Bu^n, Bu^t, Ph, TMS

Scheme 268



Ar = Ph, *p*-MeC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-HOC$_6$H$_4$
X = Br, I

variety of internal alkynes. As occurred in the precedent example, the vinylic moiety of the starting ester added preferentially to the less hindered end of the carbon−carbon triple bond, the presence of a substituent at the 3-position increasing the regioselectivity. More recently, Tanaka et al. described the same type of heteroannulation but involving β-chloro-α,β-unsaturated esters and internal alkynes in the presence of $Pd(PPh_3)_2Cl_2$ and Et_3N in toluene at 120 °C, the expected 4,5,6-trisubstituted 2*H*-pyran-2-ones being obtained in 44−74% yield.[333]

Alternatively, isocoumarins could be prepared by the palladium-catalyzed cyclization of *o*-ethynylbenzoic acids in the presence of triethylamine. However, competitive formation of the corresponding phthalides was observed for benzoic acids bearing bulky substituents at the end of the triple bond, such as Bu^t, Ph, or TMS (Scheme 267).[144] Higher regioselectivity toward the formation of the phthalides (40−90% yield) was described by Rossi et al. in the cyclization−coupling of 2-(1-alkynyl)benzoic acids with heteroaryl halides in the presence of the catalytic system $Pd(PPh_3)_4$−K_2CO_3−MeCN at 70 °C.[329b]

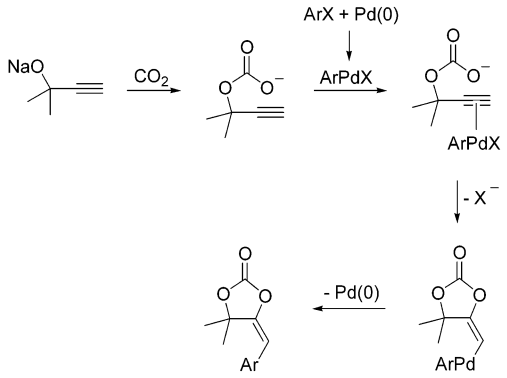
Stereodefined cyclic alkenylidene carbonates [i.e., (*E*)-benzylidenedioxolanones] were synthesized by the palladium(0)-catalyzed carboxylative cyclization−coupling of sodium α-ethynyl tertiary alkoxides and aryl halides under 10 atm CO_2 (Scheme 268).[334] By using the lithium alkoxide instead of the sodium alkoxide, allyl acetate and chloride provided the cyclic butenylidene carbonates in low yield (15−16%), whereas internal propargyl alcohols failed in this reaction. A reaction mechanism was proposed in which the alkoxide reacts with CO_2 to form a carboxylate anion that intramolecularly attacks the palladium(II)-activated alkyne moiety, followed by reductive elimination (Scheme 269). When CO was incorporated to the reaction mixture, the decarboxylative transformation of the corresponding cyclic carbonate afforded bullatenone.[335]

4.4. Other Catalysts

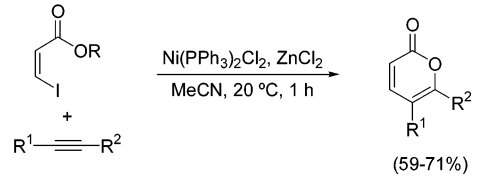
4.4.1. Nickel

In relation with the above-described synthesis of pyrones, Takahashi et al. observed that the nickel

Scheme 269



Scheme 270



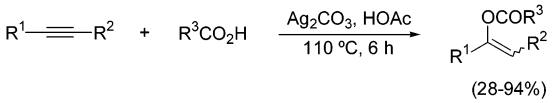
R^1 = R^2 = Et, Pr^n
R^1 = TMS; R^2 = Bu^n
R^1 = TMS; R^2 = Pent^n

complex $Ni(PPh_3)_2Cl_2$ could also catalyze the formation of 5,6-disubstituted pyrones by the coupling−cyclization reaction of (*Z*)-3-iodopropenoate with internal alkynes at room temperature (Scheme 270).[336] It was necessary to add zinc chloride to the reaction mixture in order to achieve good yields. The reaction with nonsymmetrically TMS-substituted alkynes gave a mixture of regioisomers with opposite regioselectivity to that observed for the palladium-catalyzed reaction (see Schemes 265 and 266).[146,332] A similar reaction mechanism to that of the palladium-catalyzed reaction was assumed.[332]

4.4.2. Silver

To the best of our knowledge, only the report by Ishino et al. covers the silver-catalyzed intermolecular addition of carboxylic acids to alkynes.[337] Silver carbonate exhibited the best reactivity as catalyst for a variety of internal and terminal alkynes, though the regioselectivity and yields of the corresponding enol esters were low in the latter case (Scheme 271).

Scheme 271

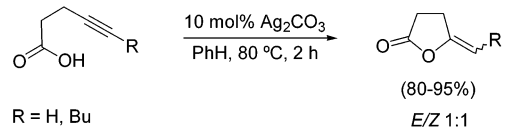


R^1, R^2 = H, Ph, CO_2Me, CH_2OH, CH_2OCOMe, CH_2OMe
R^3 = Me, Et, Pr^n, Ph

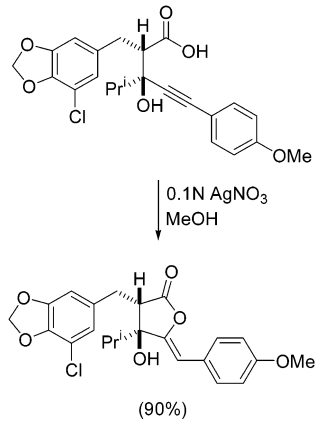
The stereoselectivity of the reaction remained unclear. A mechanism involving electrophilic addition of silver cation to the carbon−carbon triple bond forming a π-complex, followed by nucleophilic attack of the carboxylate anion, and protonolysis was suggested to account for the formation of the products.

On the other hand, around the early 1960s, different groups discovered the catalytic effect and directive influence of silver ions upon cyclization of

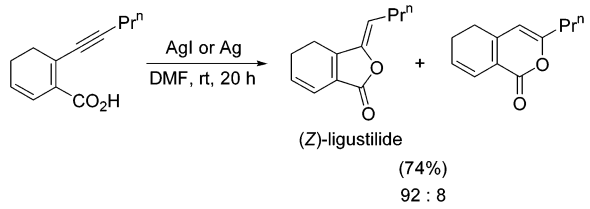
Scheme 272



Scheme 273



Scheme 274



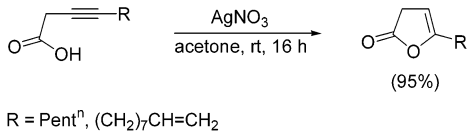
4-alkynoic acids[338] and in particular in the cyclization of *o*-carboxytolanes[339] and alkylpropargylidenemalonic acids.[340] Variable ratios of regioisomers were obtained depending on the reaction conditions.

However, Pale et al. described the highly regioselective cyclization of 4-pentynoic and 4-nonanoic acids to the corresponding γ-alkylidene lactones in high yields (Scheme 272).[259] Unfortunately, the lactone derived from 4-nonanoic acid was obtained as a 1:1 mixture of diastereoisomers.

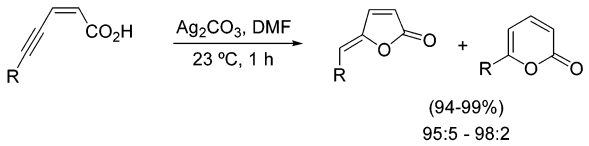
In the mid 1980s, Williard et al. utilized the silver-catalyzed cyclization of 4-alkynoic acids as a key last step in the synthesis of the exocyclic γ-methylidene-γ-butyrolactone cyanobacterin, only a trace amount (<5%) of the corresponding valerolactone being obtained (Scheme 273).[341]

2-Alkynylbenzoic acids, 2-alken-4-ynoic acids, and 4-alkynoic acids were effectively cyclized by Wakamatsu et al. to the corresponding phthalides, γ-alkylidenebutenolides, and γ-alkylidenebutyrolactones with silver iodide or silver as catalysts.[342a] The high regio- and stereoselectivity of the process enabled the synthesis of (*Z*)-ligustilide under very mild reaction conditions starting from the proper alkynoic acid (Scheme 274). Concerning the heteroannulation of 2-alkynylbenzoic acids, Bellina et al. found out that the regioselectivity could be nicely controlled depending on the silver source used.[342b] Thus, reactions performed in the presence of 20 mol % $AgNO_3$ in acetone at room temperature provided 3-substituted isocoumarins as the major products, whereas stereoisomerically pure (*Z*)-3-(1-alkylidene)phthalides were the major products when the cyclization was catalyzed by 10 mol % Ag powder in DMF at 60 °C.

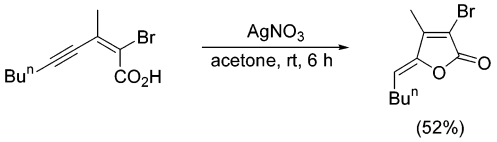
Scheme 275



Scheme 276



Scheme 277

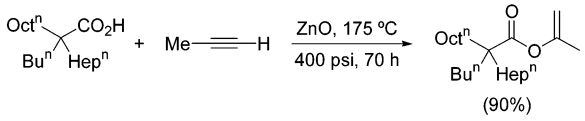


Two labile enol lactones could be also obtained by $AgNO_3$-catalyzed 5-*endo*-*dig* cyclization of 3-alkynoic acids in acetone at room temperature (Scheme 275).[343]

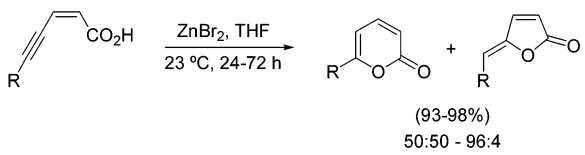
Negishi et al. subjected (*Z*)-3,5-diphenylpent-2-en-4-ynoic acid to the silver-catalyzed lactonization with silver nitrate in methanol, the expected γ-alkylidenebutenolide being obtained with higher regioselectivity (but the same stereoselectivity) than the palladium-catalyzed reaction (95:5 vs 83:6).[324] This methodology was successfully applied to the synthesis of the antibiotic lissoclinolide[344] and more recently extended to other (*Z*)-2-en-4-ynoic acids.[345] Concerning the latter report, it was confirmed that the lactonization of the (*Z*)-2-en-4-ynoic acids catalyzed by Ag_2CO_3 was superior in both yields and regioselectivity to the one-pot alkyne−alkene coupling−lactonization tandem process under Sonogashira coupling conditions [$Pd(PPh_3)_4$, CuI, Et_3N, MeCN, 23 °C, 12 h] for the selective synthesis of (*Z*)-5-alkylidene-5*H*-furan-2-ones (Scheme 276). The regioselectivity observed, opposite to that with zinc bromide (see below), was explained in terms of a stereoelectronically favored 5-*exo*-mode of cyclization where bond polarization was considered less important than in the zinc-bromide-catalyzed reaction.

Rossi et al. utilized silver nitrate as an alternative to a palladacycle as catalyst for the conversion of (*E*)-4-(1-alkynyl)-2-bromopropenoic acids into (*Z*)-3-bromo-5-ylidene-5*H*-furan-2-ones (see Scheme 262).[329] In fact, silver nitrate was the catalyst of choice to accomplish the cyclization of (*E*)-4-(1-hexynyl)-2-bromopropenoic acid under milder reaction conditions and better regioselectivity in comparison with the palladium-catalyzed reaction (Scheme 277). This catalytic system also allowed the stereocontrolled synthesis of 5-aryl- and 5 alkyl-substituted (*E*)-3-[1-(aryl)methylidene]- and (*E*)-3-(1-alkylidene)-3*H*-furan-2-ones by cyclization of the corresponding (*E*)-2-(1-alkynyl)-3-aryl(or alkyl)propenoic acids under very mild reaction conditions and in moderate to good yields (see Scheme 263).[330]

Scheme 278



Scheme 279



R = Pr^i, Bu^t, Hex^n, Cy, Ph

4.4.3. Zinc

In the early 1970s, Rothman et al. reported the conversion of 2-butyl-2-heptyldecanoic acid into the corresponding isopropenyl ester by reaction with propyne in the presence of a catalytic amount of zinc oxide. The Markovnikov addition product was obtained in good yield but under relatively harsh reaction conditions (175 °C in autoclave) (Scheme 278).[346] Isopropenyl stearate, palmitate, laurate, and phenylstearate, among others, were also prepared following this methodology.[347]

By using $ZnBr_2$ instead of Ag_2CO_3 as catalyst, Negishi et al. could drive the cyclization of (*Z*)-5-alkyl-2-en-4-ynoic acids toward the formation of the corresponding 6-alkyl-2*H*-pyran-2-ones in excellent yields and with ≈95:5 regioselectivity for most of the examples studied (Scheme 279).[345] It was suggested that polarization of the unsaturated (*Z*)-5-alkyl-2-en-4-ynoic acids would favor the formation of the 2*H*-pyran-2-ones via a Lewis-acid-catalyzed polar process (see Scheme 276 to compare).

4.4.4. Mercury

Mercury compounds were used until the mid 1980s as effective catalysts to promote the addition of carboxylic acids to alkynes, though in more recent chemistry they have been replaced by alternative less toxic catalysts. Anyhow, some contributions to this field deserve being mentioned herein. For instance, in 1955 Lemaire et al. reported the mercury-catalyzed addition of acetic acid to 3-hexyne using a solution of perchloric acid and mercury(II) acetate in anhydrous acetic acid.[348] Mercury(II) acetate but in the presence of boron trifluoride etherate was also found to catalyze the formation of diisopropenyl esters from propyne and a variety of dicarboxylic acids at room temperature in 40−85% yield.[349] Under very similar reaction conditions, acetic acid added to 1-octyne and the tosylate of 3-butyn-1-ol to afford the corresponding Markovnikov enol acetates.[350]

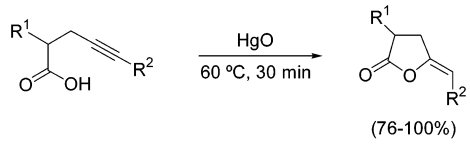
Regarding the mercury-catalyzed intramolecular addition of carboxylic acids to alkynes, Yamamoto et al. studied the cyclization of various acetylenecarboxylic acids in the presence of a catalytic amount of mercury(II) oxide to give the corresponding γ-alkylidenebutyrolactones in good to excellent yields (Scheme 280).[351] The reaction proceeded regioselectively, mainly affording the (*Z*)-enol lactone.

γ-Methylidene-γ-butyrolactone (α′-angelicalactone) was prepared in 74% yield by Katzenellenbogen et al. by cyclization of 4-pentynoic acid in dichloromethane and with a catalytic amount of mercury(II) acetate.[352] When several 2-alkylidene-3-hydroxy-4-alkynoic esters where saponified and cyclized under mercury(II) catalysis, the corresponding α-alkylidene-β-hydroxy-γ-butyrolactones were obtained (Scheme 281).

Further investigations in this field showed that mercury(II) trifluoroacetate was more efficient than mercury(II) acetate in catalyzing the lactonization of differently substituted 4-alkynoic acids (Scheme 282).[353] Cyclization of the 5-bromo and 5-chloro derivatives led stereospecifically to the corresponding (*Z*)-enol lactones but quite slowly. On the other hand, cyclization of unsubstituted or 5-methyl- or 5-trimethylsilyl-substituted 4-pentynoic acids was faster, albeit isomerization occurred probably by readdition of mercury to the carbon−carbon double bond of the lactones. Cyclization of 5-iodo-4-pentynoic acid was also accomplished with the $Hg(OCOCF_3)_2$−CH_2Cl_2 catalytic system to provide (*Z*)-5-(iodomethylidene)-tetrahydro-2-furanone in 20% yield after 52 h at room temperature.[354]

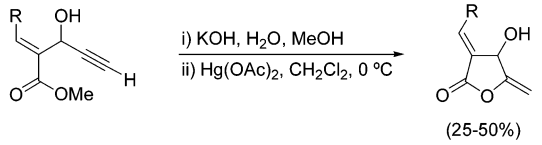
The above-shown methodology allowed the lactonization of either (2*R**,3*R**)-acetamido or -benzamido acetylenic acids to give the corresponding 3,4-*trans*-diprotiolactones in good yields (Scheme 283).[355] Unfortunately, treatment of the (2*R**,3*S**)-isomers with either $Hg(OCOCF_3)_2$ or Hg(OAc) led to a 1:1 mixture of diastereoisomers in low yield.

Scheme 280



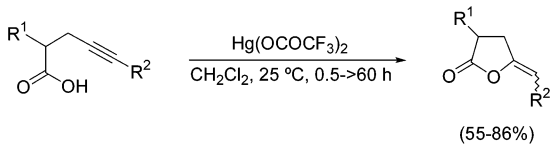
R^1 = H, Ph, CH$_2$C≡CPh, MeC(OCH$_2$CH$_2$O)
R^2 = H, Ph

Scheme 281



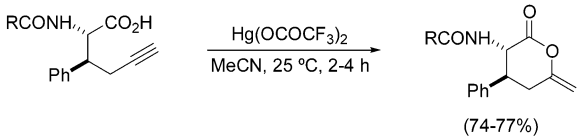
R = CH$_2$=CH(CH$_2$)$_9$, Me(CH$_2$)$_{12}$, Me(CH$_2$)$_{14}$

Scheme 282



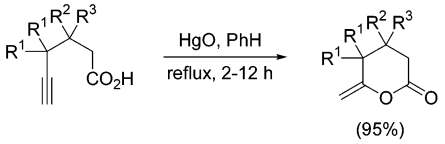
R^1 = H, Ph
R^2 = H, D, Me, Br, Cl, TMS

Scheme 283



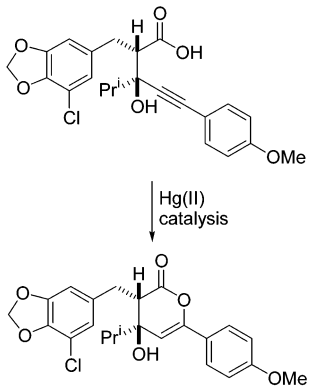
R = Me, Ph

Scheme 284



$R^1 = R^3 = H$; $R^2 = Me$
$R^1 = R^2 = Me$; $R^3 = H$
$R^1 = H$; $R^2 = R^3 = Me$
$R^1 = R^3 = H$; $R^2 = Ph$
$R^1 = R^2 = R^3 = Me$

Scheme 285



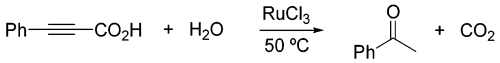
It was also found that mercury(II) oxide catalyzed the cyclization of substituted 5-hexynoic acids to form the expected δ-methylidene-δ-lactones in excellent yields (Scheme 284).[356]

Finally, and in contrast with the results obtained with silver nitrate (see Scheme 273), the mercury(II)-catalyzed cyclization of the precursor of cyanobacterin led to the corresponding valerolactone instead of the exocyclic γ-methylidene-γ-butyrolactone obtained under silver catalysis (Scheme 285).[341]

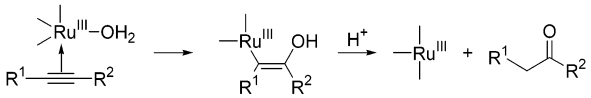
5. Hydration

The hydration of activated alkynes follows Markovnikov's rule, so only acetylene gives an aldehyde.[357] For a long time the hydration of acetylene has been a reaction of a major industrial interest. In fact, before the advent of the Wacker process, acetaldehyde was essentially produced by the hydration of acetylene. All other alkynes different from acetylene give ketones, alkynes of the type RC≡CH forming methyl ketones almost exclusively, whereas for alkynes of the type RC≡CR′ both regioisomers can be obtained. Although the hydration of alkynes[172,358] can be effected under acid catalysis,[359] the reactions are usually sluggish except for very reactive alkynes. Since the discovery of acceleration of alkyne hydration in the presence of mercury(II) ions (Kucherov reaction),[360] a wide variety of mercury(II) compounds have been employed as catalysts, mainly in aqueous acid solutions: $HgSO_4-H_2SO_4-H_2O$,[361] $Hg(ClO_4)_2-HClO_4-H_2O$,[362] $(MeHg)_2SO_4-H_2SO_4-H_2O$,[363] $Hg(OAc)_2-THF-H_2O$,[364] $HgO-H_2SO_4-H_2O$,[365] or $Hg(OAc)_2-MeOH-HOAc$.[366] Ion-exchange resins containing Hg(II)[367] or other ions such as Cu(I), Zn(II), and Cd(II)[368] were also effective catalysts for alkyne hydration, whereas some mercury-free catalysts based on the mixed Cd−Ca phosphates were shown to be highly active, selective, and long-living catalysts for the vapor-phase hydration of acetylene to acetaldehyde.[369] Cadmium phosphate and vanadate,[370] chromium and zirconium phosphates,[371] calcium phosphate−copper phosphate,[372] as well as the cobalt, nickel, zinc, cadmium, and mixed calcium−cadmium, cobalt−zinc phosphomolybdates[373] also found application in the latter mentioned process. The title reaction has been studied also, above all from that kinetic point of view, on zeolite catalysts containing a variety of transition-metal ions as the active sites.[374] Other catalysts used for acetylene hydration are $PdSO_4$, $Fe_2(SO_4)_3$,[375] and a catalyst containing CuCl together with ammonium chloride, hydrochloric acid, and metal sulfide additives.[376]

Scheme 286



Scheme 287



Since most of the literature presented above is rather old and refers mainly to the use of toxic mercury catalysts and to the hydration of acetylene, from this point we will try and focus on the more modern reports dealing with the hydration of other alkynes (where different regioisomers can be obtained) under the catalysis of mainly noble metals such as ruthenium, palladium, and platinum.

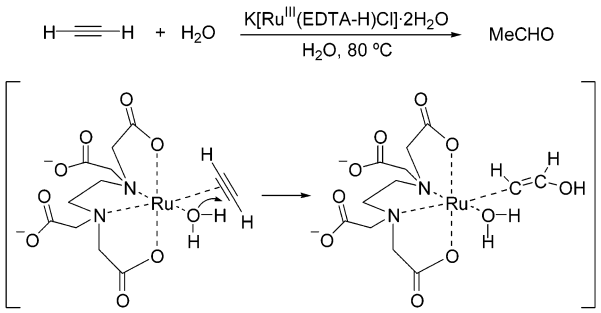
5.1. Ruthenium Catalysts

In the early 1970s, Halpern et al. demonstrated that ruthenium(III) chloride was an effective catalyst for the hydration of acetylene and mono- and disubstituted alkynes under relatively mild reaction conditions.[377] Thus, methylacetylene, ethylacetylene, and phenylpropiolic acid were converted into acetone, ethyl methyl ketone, and acetophenone, respectively, the latter derived from decarboxylation of the corresponding β-keto acid (Scheme 286). It was suggested that water was delivered from the coordination sphere of ruthenium in a π-complex to the activated carbon−carbon triple bond followed by protonolysis (Scheme 287).

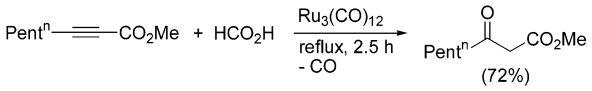
Khan et al. reported in 1990 the hydration of acetylene catalyzed by the water-soluble complex $K[Ru^{III}(EDTA\text{-}H)Cl]\cdot 2H_2O$ to give cleanly acetaldehyde.[378] A reaction mechanism similar to that shown in the previous scheme was proposed involving a π-complex intermediate with a water molecule coordinated to the metal ion (Scheme 288).

The hydration of alkynes could be performed in an anhydrous medium using formic acid as a water donor. Functionalized alkynes, particularly those oxygenated, were inert to formic acid but could be activated with $Ru_3(CO)_{12}$.[379] For instance, methyl 2-octynoate gave the expected methyl 3-oxooctanoate under $Ru_3(CO)_{12}$ catalysis with further transformation into 2-heptanone by prolonging the reaction time (Scheme 289).

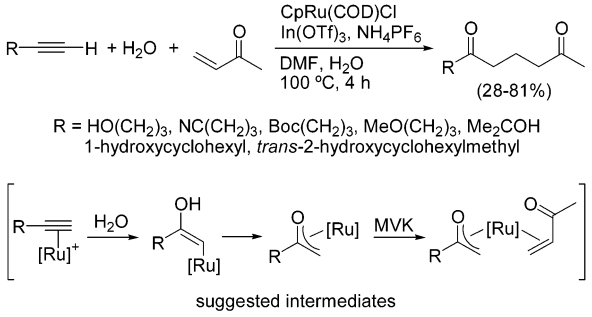
Scheme 288



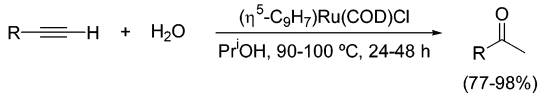
Scheme 289



Scheme 290



Scheme 291

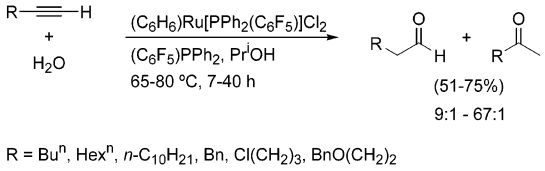


On the basis of the Markovnikov addition of water to ruthenium-activated alkynes, Trost et al. developed a three-component addition reaction leading to 1,5-diketones consisting of a terminal alkyne, water, and methyl vinyl ketone (MVK) in the presence of CpRu(COD)Cl and indium triflate (Scheme 290).[380] A ruthenium−enolate-based plausible mechanism was proposed in which the conjugate addition steps were faster that the protonation of the ruthenium enolate.

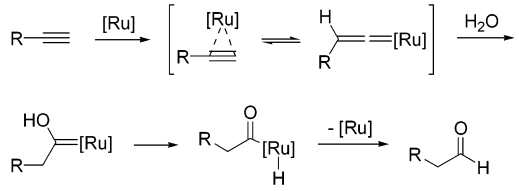
In the presence of indenyl ruthenium(II) complex (η^5-C_9H_7)Ru(COD)Cl, several aliphatic terminal alkynes and phenylacetylene underwent the addition of water to afford the corresponding ketones in high yield (77−98%) and selectivity (92−98%) (Scheme 291).[381] According to the authors, this is the first ruthenium(II) catalyst active in the hydration of a α-hydroxyalkyne to form the corresponding ketone.

Wakatsuki et al. described the first example of anti-Markovnikov hydration of terminal alkynes catalyzed by ruthenium(II) complexes in the presence of phosphine ligands.[56,382] The optimum reaction conditions involved the addition of 10 mol % of $(C_6H_6)Ru[PPh_2(C_6F_5)]Cl_2$ and 30 mol % of $(C_6F_5)PPh_2$ to a solution of the 1-alkyne in 2-propanol (Scheme 292). The method found application to a wide range

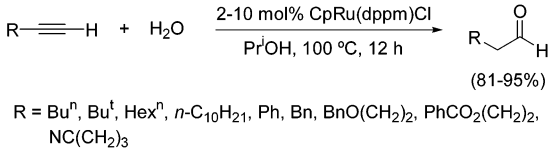
Scheme 292



Scheme 293



Scheme 294

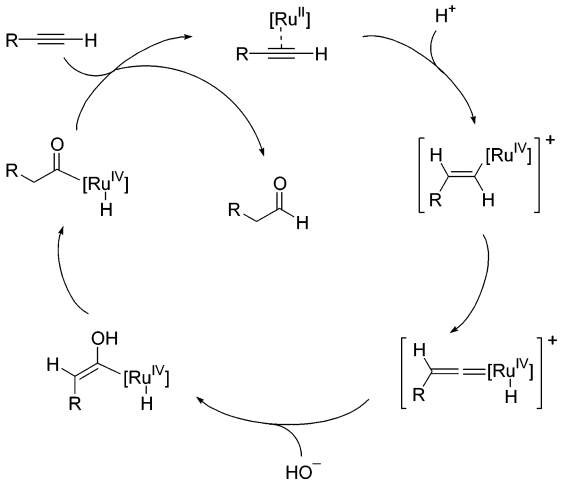


of alkynes, but *tert*-butylacetylene and phenylacetylene gave only trace amounts of the corresponding aldehydes. A plausible reaction mechanism was proposed based on related stoichiometric processes,[383] including initial tautomerization of a π-complex to a vinylidene complex followed by nucleophilic attack by water at the vinylidene α-carbon atom to form a hydroxycarbene and then an acyl intermediate, the latter providing the aldehyde by reductive elimination or protonolysis (Scheme 293). The authors believe that the role of the added phosphine was to shift the equilibrium in favor of the vinylidene complex[384] and to retard the decarbonylation of the acyl intermediate.

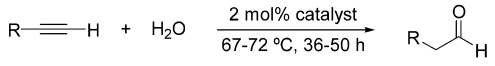
A dramatic improvement of both activity and selectivity in the above reaction was observed by using cyclopentadienylruthenium complexes bearing bidentate or monodentate phosphine ligands.[385] For instance, the reaction of 1-hexyne with water in the presence of 1 mol % of CpRu(dppm)Cl in 2-propanol at 100 °C for 12 h gave hexanal quantitatively without any byproduct (Scheme 294). Even *tert*-butylacetylene and phenylacetylene reacted cleanly and in high yield (81% and 90%, respectively) under these reaction conditions.

Further insight into the reaction mechanism based on the isolation of organic and organometallic byproducts, deuterium-labeling experiments, and DFT calculations revealed the participation of a metal−acyl intermediate. It was also concluded that the final formyl hydrogen comes from the original acetylenic hydrogen and that Ru(II)−vinylidene species are not involved in the pathway.[386] The new mechanistic proposal includes (a) proton attack from water at the substituted carbon of a Ru(II)−η^2-coordinated alkyne, (b) α-hydrogen migration to the metal center to form a Ru(IV)−hydride−vinylidene intermediate, (c) attack of the hydroxyl anion at the α-carbon of the vinylidene, and (d) reductive coupling of the resulting acyl group and hydride to give the aldehyde and the Ru(II) species (Scheme 295).

Scheme 295

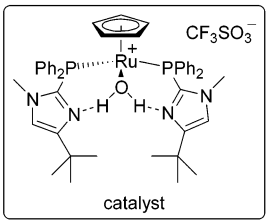


Scheme 296

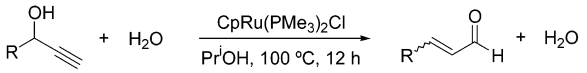


(54-98%)

R = Bu^n, Bu^t, Ph, $Ph(CH_2)_2$, $TBDMSOCH_2$, $THPOCH_2$, $NC(CH_2)_3$



Scheme 297



(75-96%)

E/*Z* 80:20-94:6

R = Me, Et, $Pent^n$, Bu^nCHEt, Cy, Ph

Parallel to the work by Wakatsuki, Grotjahn et al. reported the highly selective anti-Markovnikov hydration of terminal alkynes in the presence of a ruthenium(II) catalytic system that does not need electron-rich phosphines and that tolerates acid-sensitive propargylic ether substituents and nitriles (Scheme 296).[387] The best results were obtained for alkyl-substituted alkynes, the reaction being more sluggish for *tert*-butylacetylene and phenylacetylene. It was suggested that the presence of the imidazole groups in the catalyst played a key role in the catalysis.

By using $CpRu(PMe_3)_2Cl$ as catalyst, propargyl alcohols in aqueous solutions were transformed into the corresponding α,β-unsaturated aldehydes in high yields and in a stereoselective manner (Scheme 297).[388] The whole reaction could be considered as an anti-Markovnikov hydration at the terminal alkyne carbon with concomitant dehydration of the original hydroxy group, mainly affording the (*E*)-stereoisomers.

Gimeno et al. found a very elegant way to control the regioselectivity in the addition of water to terminal alkynes. Thus, the presence of the π-acidic COD ligand in the indenyl ruthenium(II) complex (η^5-C_9H_7)Ru(COD)Cl favored a π-alkyne intermediate that directed the addition of water in a Markovnikov fashion (see Scheme 291). In contrast, the electron-rich bisphosphine complex (η^5-C_9H_7)Ru(PPh_3)$_2$Cl, which was expected to favor a vinylidene intermediate, drove the addition of water to both terminal alkynes and propargyl alcohols in an anti-Markovnikov manner when the reaction was performed at 60 °C in an aqueous micellar environment.[389] The presence of a surfactant (SDS or CTAB) allowed the reaction to take place within the micelle, aggregating both the catalyst and substrate and improving the yields and selectivity with respect to the aqueous 2-propanol system.

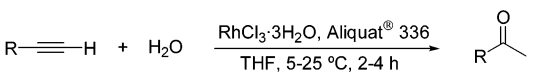
5.2. Rhodium Catalysts

James et al. reported in the late 1960s the catalytic hydration of alkynes under mild conditions with aqueous acid solutions of rhodium(III) chloro complexes of the type $[Rh(H_2O)_{6-n}Cl_n]^{(n-3)-}$.[390] Species with $n = 0$ were found to be completely inactive, the activity increasing up to a maximum at $n = 5$, while the hexachloro complex was also inactive. Thus, acetylene was converted to acetaldehyde at 60 °C and 1 atm pressure, whereas phenylpropiolic acid gave acetophenone due to decarboxylation of the expected β-ketoacid. These rhodium(III) catalytic systems behaved similarly to the above-described ruthenium systems (see Schemes 286 and 287),[377] but for acetylene itself, $RhCl_3 \cdot 3H_2O$ in 3 M HCl was about three times more reactive than the corresponding system involving ruthenium(III) chloride.

Blum et al. observed that the ion pairs generated from $RhCl_3 \cdot 3H_2O$ and the quaternary ammonium salt Aliquat 336 promoted the addition of water to terminal alkynes to form exclusively ketones.[391] Both aliphatic and aromatic terminal alkynes were found to react at reasonable rates though in low yields, internal alkynes reacting very slowly or not at all (Scheme 298). The quaternary ammonium ions seemed to function not only as phase-transfer agents but also as essential parts of the active catalyst. As a major advantage of this method, the rhodium catalyst could be recovered as $NaRhCl_4$ in the aqueous phase by treatment with aqueous $NaClO_4$. The results obtained were explained according to the general reaction mechanism proposed by James and Rempel.[390]

The above research group also found that a polystyrene-supported ion pair, obtained from $RhCl_3$ and the Dowex 1 ion exchanger, acted as a highly active and recyclable catalyst in the hydration of aromatic alkynes (Scheme 299).[392] The addition followed Markovnikov's rule, affording the expected acetophenones together with variable amounts of oligomerization products (5−20%).

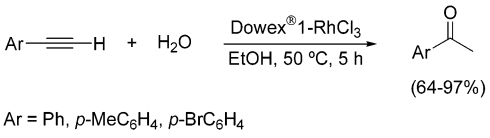
Scheme 298



(19-23%)

R = Hex^n, Hep^n, Ph, Bn, $Ph(CH_2)_2$, $Ph(CH_2)_3$

Scheme 299



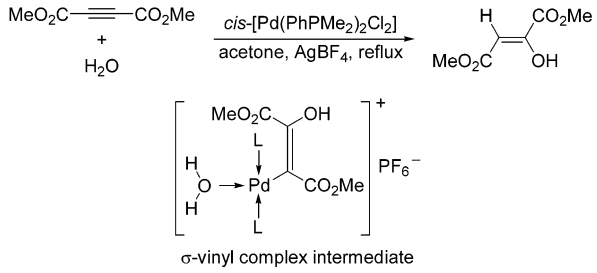
5.3. Palladium Catalysts

cis-[Pd(PhPMe$_2$)$_2$Cl$_2$], utilized by Parkins et al. to catalyze the addition of methanol to dimethyl acetylenedicarboxylate (see Scheme 131), also found application in the hydration of this substrate with complete conversion into oxalacetic acid dimethyl ester, which exists predominantly in the enol form at room temperature (Scheme 300).[195] The *trans*-addition mode was explained by H_2O attack from outside the coordination sphere, the resulting vinyl complex being protonolized in the acidic reaction medium.

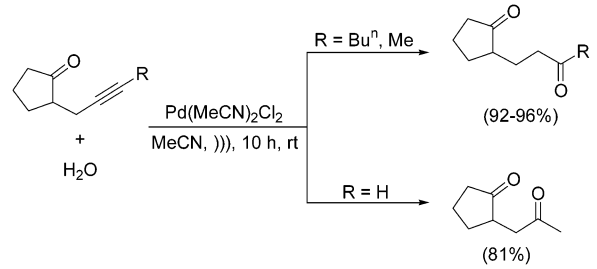
A series of diketones were regioselectively prepared by Utimoto et al. by palladium(II)-catalyzed hydration of alkynyl ketones under mild reaction conditions.[393] The regioselectivity was controlled by carbonyl-group participation and depended on the substituents on the alkyne moiety. For instance, hydration of 2-(2-heptynyl)cyclopentanone led to the corresponding 1,5-diketone 2-(3-oxoheptyl)cyclopentanone, whereas a 1,4-diketone was selectively formed from the terminal acetylene 2-(2-propynyl)cyclopentan-1-one (Scheme 301). The synthetic utility of this methodology was demonstrated in the regioselective hydration of 5,6-didehydroprostaglandin E_2 and in the synthesis of substituted furans.[394]

Cacchi et al. described the conversion of vinyl triflates into γ'-hydroxy-α,β-enones through the palladium-catalyzed coupling with 1-butyn-4-ols, followed by reaction of the resulting 1-hydroxy-3-yn-5-enes with an acidic CH_2Cl_2−3 N HCl system in the presence of the TBAC−$PdCl_2$ combination (Scheme 302).[395] Alternatively, the whole transformation could be effected in a one-pot process without isolation of the corresponding 1-hydroxy-3-yn-5-enes and was

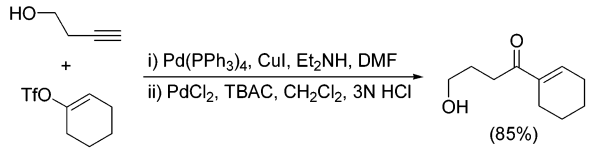
Scheme 300



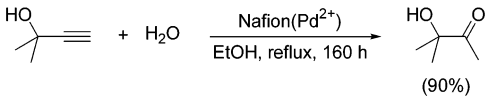
Scheme 301



Scheme 302



Scheme 303



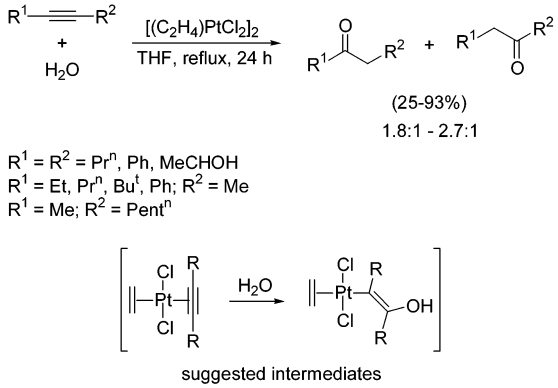
applied to a large variety of structurally different vinyl triflates. It was presumed that a σ-vinylpalladium species formed derived from the intramolecular cyclization of the 1-hydroxy-3-yn-5-ene intermediate.

A partially exchanged Nafion(Pd^{2+}) resin catalyst was shown to be active for the hydration of several alkynes such as 2-methyl-3-butyn-2-ol, the expected 3-hydroxy-3-methyl-2-butanone being obtained as the sole product in high yield (Scheme 303).[396] Although phenylacetylene also could be transformed into acetophenone in high yield, the reactions were very slow, requiring in all cases more than 5 days under reflux.

5.4. Platinum Catalysts

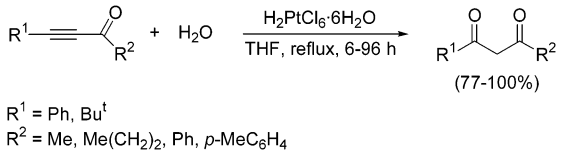
In a paper by Chatt et al. in 1961 dealing with the preparation of alkyne derivatives of Pt(II) complexes, it was reported that ethanolic $Na_2PtCl_4 \cdot 4H_2O$ reacted with several alkynes to form ketones.[397] However, it was in the early 1990s when Jennings et al. demonstrated that Zeise's dimer was an active and selective catalyst in the hydration of several unactivated alkynes.[398] Except for 1-hexyne, modest regioselectivity was observed for unsymmetrically substituted alkynes, the presence of electron-withdrawing substituents severely retarding the reaction (Scheme 304). Better regioselectivity was observed for alkynes

Scheme 304



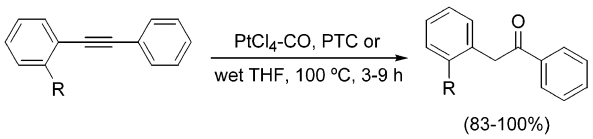
bearing carbonyl groups, which was rationalized in terms of a combination of Lewis-acid catalysis and chelation control.[398b] The main drawback of Zeise's dimer is that it is expensive or must be prepared through an inconvenient procedure. Although simple and readily available platinum compounds such as $PtCl_2$, $PtBr_2$, and PtI_2 were also effective in the hydration of some internal alkynes, the regioselectivity was again moderate.[399]

Scheme 305



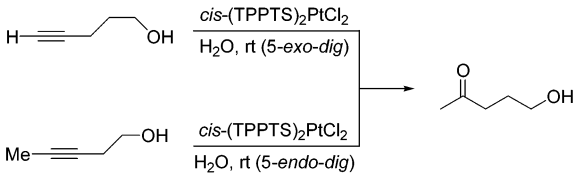
R^1 = Ph, Bu^t
R^2 = Me, $Me(CH_2)_2$, Ph, *p*-MeC_6H_4

Scheme 306



R = Me, Br

Scheme 307

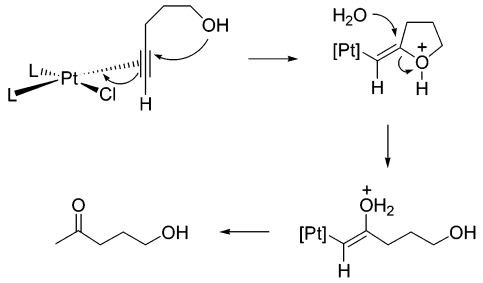


The platinum(IV) compound $H_2PtCl_6 \cdot 6H_2O$ was successfully utilized by Blum et al. in the catalytic hydration of a series of alkynones to give the corresponding 1,3-diketones and their corresponding enol tautomers (Scheme 305).[400] The reaction was found to proceed more slowly than for monoarylated and nonaromatic alkynes.

A wide range of aliphatic and aromatic alkynes were hydrated using the complex generated from $PtCl_4$ and CO as catalyst, both under homogeneous and phase-transfer conditions (PTC).[401] Both terminal and internal alkynes reacted almost equally well, terminal alkynes following Markovnikov's rule. Unhindered alkylarylacetylenes furnished mixtures of ketones, prevailing those having the carbonyl group adjacent to the aliphatic moiety. Very high regioselectivity was observed for nonsymmetrical diarylacetylenes with major formation of the ketones in which the carbonyl group is remote from the bulky moieties (Scheme 306). Very good yields were also obtained for functionalized alkynes, diynes, and triynes. The authors suggested that $HPtCl(CO)_2$ was the active catalyst in the hydration process, taking part in a mechanism similar to that with Zeise's dimer. Very interesting was the immobilization of the $PtCl_4-CO$ catalyst on a styrene−divinylbenzene copolymer or encapsulation in a silica sol−gel matrix, which provided about 50% yield of acetophenone by hydration of phenylacetylene and possessed the advantage of being reusable.[402]

Atwood et al. developed a platinum(II) complex bearing a sulfonated phosphine as water-soluble ligand, *cis*-$(TPPTS)_2PtCl_2$ [TPPTS = tris(sodium *m*-benzenesulfonate)phosphine], as an effective hydration catalyst for the water-soluble alkynes 4-pentyn-1-ol and 3-pentyn-1-ol (Scheme 307).[403] Both reactions were regiospecific to produce the same product 5-hydroxy-2-pentanone as a result of 5-*exo*-*dig* and 5-*endo*-*dig* cyclization steps, respectively, involved in the reaction mechanism. Scheme 308 shows the reaction mechanism for 4-pentyl-1-ol. Under the same reaction conditions, 5-hexyn-1-ol gave 6-hydroxy-2-hexanone in 100% yield. Alternatively, water-soluble bidentate phosphine ligands also could be used to catalyze the hydration of the above substrates.[404]

Scheme 308



5.5. Other Catalysts

5.5.1. Iridium

Chin et al. studied in detail for the first time the hydration of alkynes with water-soluble metal complexes of sulfonated tertiary phosphines. In particular, $(TPPTS)_2(CO)IrCl \cdot xH_2O$ was found to catalyze the hydration of terminal alkynes at room temperature and in MeOH as solvent (Scheme 309).[405] The hydration of acetylene was much faster than that of terminal alkynes. However, diphenylacetylene did not undergo hydration except at 100 °C and in very low yield.

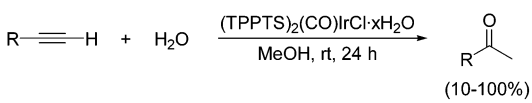
5.5.2. Copper

Copper(II) triflate and tetrafluoroborate catalyzed the hydration of 2-methyl-3-butyn-2-ol under homogeneous conditions to form 3-hydroxy-3-methyl-2-butanone in almost quantitative yield (see Scheme 303). Alternatively, a heterogeneous catalytic system based on a complete exchanged Nafion(Cu^{2+}) resin catalyst allowed the hydration of several terminal alkynes and 4-octyne to give the corresponding ketones in moderate to good yields, though long reaction times were required (Scheme 310).[396] Other ion-exchange resins with more strongly coordinating anions, such as Amberlite IRC84(Cu^{2+}) (RCO_2^-) or Dowex-50W(Cu^{2+}) (RSO_3^{2-}), were not efficient hydration catalysts.

5.5.3. Gold

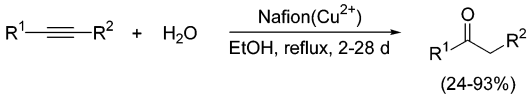
Utimoto et al. discovered that better results in the hydration of certain alkynyl ketones were obtained

Scheme 309



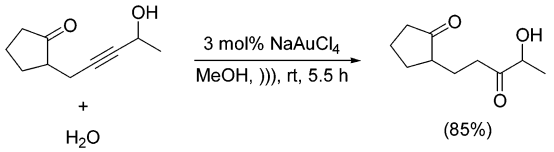
R = H, $Pent^n$, Ph, $ClCH_2$, $MeOCH_2$, $HC{\equiv}C(CH_2)_4$

Scheme 310

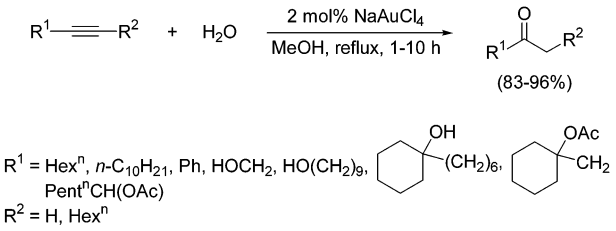


R^1 = Ph, EtC(Me)OH, Hex^n; R^2 = H
$R^1 = R^2 = Pr^n$

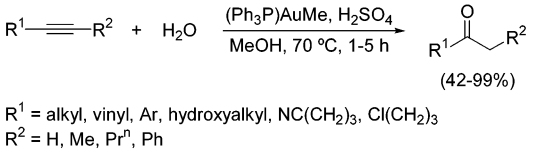
Scheme 311



Scheme 312



Scheme 313



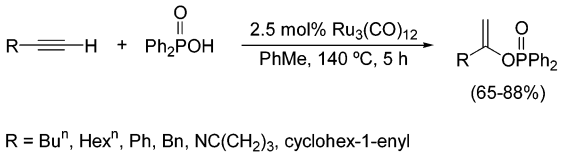
when the reaction was performed in the presence of a gold catalyst instead of a palladium catalyst (see one example in Scheme 311).[393] In refluxing aqueous methanol, a variety of terminal alkynes were hydrated under gold(III) catalysis to furnish the expected ketones in excellent yields (Scheme 312).[406] Internal alkynes were also smoothly hydrated but giving nearly a 1:1 mixture of regioisomers. On the other hand, methyl propargyl ethers were transformed into α,β-unsaturated ketones regioselectively under the above reaction conditions.[407]

Hayashi, Tanaka et al. reported that the Au(I)−acid catalytic system in aqueous methanol was a powerful catalyst to promote the hydration of a large variety of alkynes with turnover frequencies of at least 2 orders of magnitude higher than *cis*-$(TPPTS)_2PtCl_2$.[408] Thus, aliphatic and aromatic terminal alkynes, including those bearing functional groups such as alkoxy, cyano, chloro, and olefinic moieties, underwent hydration in moderate to excellent yields to form only the Markovnikov products (Scheme 313). Internal alkynes displayed lower reactivity, presumably because of steric hindrance.

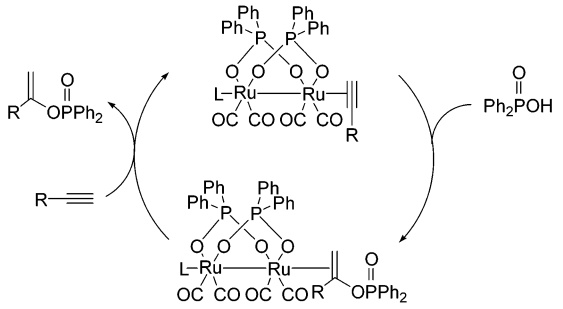
6. Addition of Other Oxygenated Nucleophiles

As shown above, the metal-catalyzed addition reaction of O−H bonds of alcohols, carboxylic acids, and water to alkynes has been actively studied. However, to the best of our knowledge, the analogous reactions with phosphinic acids have been explored only by Tanaka et al., the resulting alkenyl phosphinates being of potential synthetic utility.[409] This group reported the ruthenium-catalyzed addition reaction of diphenylphosphinic acid to terminal alkynes to give the corresponding Markovnikov products in good yields and high regioselectivities (Scheme 314).[410] The best results were obtained with $Ru_3(CO)_{12}$ complex, which in addition allowed the introduction of two phosphinate groups over 1,8-nonadiyne and did not react with the nitrile and olefinic functionalities. Dimeric ruthenium species were proposed to be involved in the reaction mechanism (Scheme 315).

Scheme 314



Scheme 315



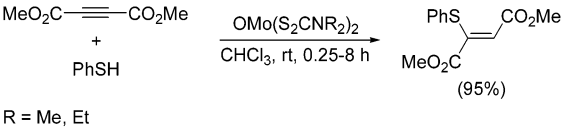
7. Hydrothiolation and Hydroselenation

Vinyl sulfides are compounds of enormous synthetic utility.[411] However, the transition-metal-catalyzed addition of thiols and selenols to alkynes[412] has not received much attention, probably due in part to the widespread prejudice that this type of compound is considered as a catalyst poison. Nonetheless, in general, this reaction provides better yields and complementary or better selectivities when compared with the radical addition processes (leading to anti-Markovnikov products)[413] or with the noncatalyzed nucleophilic addition of thiolate anion (leading to Markovnikov products), where relatively longer reaction times or more severe conditions are essential.[414]

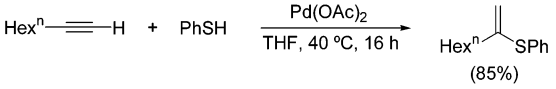
7.1. Intermolecular Processes

To the best of our knowledge, the first transition-metal-catalyzed addition of thiols to alkynes was reported by Newton et al. in 1976.[415] In particular, the addition of PhSH to DMAD in a 1:1 molar ratio, catalyzed by *cis*-dioxo-bis(*N*,*N*-dialkyldithiocarbamato)molybdenum(VI) $[MoO_2(S_2CNR_2)_2$, (R = Me, Et)] or oxobis(*N*,*N*-dialkyldithiocarbamato)molybdenum-(IV) $[OMo(S_2CNR_2)_2$, (R = Me, Et)], afforded stereospecifically the monoaddition product dimethyl 2-(phenylthio)fumarate in 95% yield (Scheme 316). Diaddition products were obtained when a 2-fold excess of PhSH was present in the reacting medium. From a mechanistic point of view, the authors suggested that the oxomolybdenum catalyst did not function by simple activation of the carbon−carbon

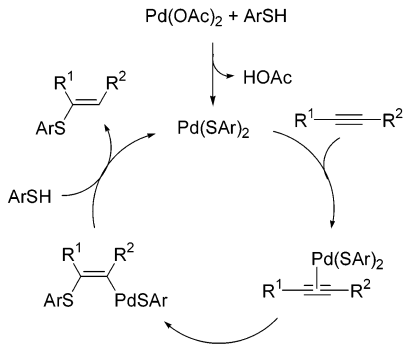
Scheme 316



Scheme 317



Scheme 318



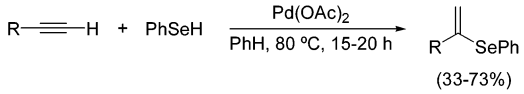
triple bond in the alkyne but probably by its polarization by complexation to the carbonyl group.

Reger et al. reported in 1984 the activation of the carbon−carbon triple bond in dialkyl acetylenes by iron complexes toward the nucleophilic addition of sodium thiophenolate, yielding η^1-alkenyl complexes.[416] However, the first clear example of hydrothiolation of alkynes catalyzed by different transition-metal complexes was described by Ogawa and Sonoda et al. in 1992.[417] Among the catalysts studied, $Pd(OAc)_2$ was shown to give the best yield and selectivity toward the Markovnikov product in the addition of thiophenol to 1-octyne (Scheme 317). $Pt(PPh_3)_4$ and $Pd(PhCN)_2Cl_2$ required higher temperatures and as a result led to a product with isomerization of the carbon−carbon double bond. A similar behavior was observed for $Pd(PPh_3)_4$, which exhibited lower reactivity than palladium(II) complexes. $Ni(PPh_3)_2Cl_2$ was a poor catalyst, whereas $Rh(PPh_3)_3Cl$ led mainly to the regioisomeric anti-Markovnikov product. The reaction was applied to other aromatic thiols and a variety of terminal alkynes, including propargyl alcohols and amines, and trimethylsilylacetylene, an enyne reacting only across the carbon−carbon triple bond. Internal alkynes furnished the *syn*-addition products, the regioisomeric and diastereomeric ratio depending on the structure of the substrate.

The above type of reaction was rationalized through a mechanistic proposal involving the formation of $Pd(SAr)_2$, alkyne insertion into the Pd−S bond, and protonolysis of the Pd−C bond under the action of ArSH (or HOAc) (Scheme 318). The cleavage of the Pd−C bond in the vinylpalladium intermediate can explain the low activity of *p*-MeC_6H_4SH or *p*-$MeOC_6H_4SH$, the acidity of which should be much lower than that of PhSH. On the other hand, protonolysis can be effected by HOAc to regenerate $Pd(OAc)_2$. As a plausible competitive route, the vinylpalladium intermediate could undergo reductive elimination, giving $R^1(ArS)C{=}C(SAr)R^2$ and Pd(0), as described by the authors for the addition of PhSSPh to alkynes under Pd(0) catalysis.[418]

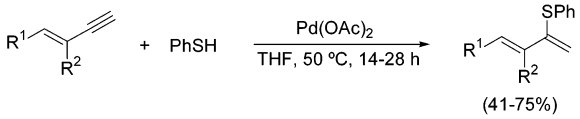
The same research group also described the first example of transition-metal-catalyzed hydroselenation of alkynes.[419] As in the case of hydrothiolation,

Scheme 319



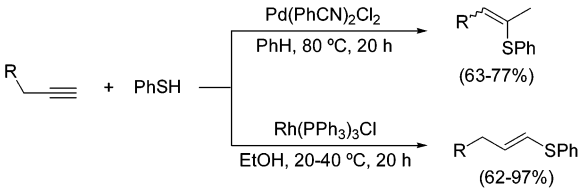
R = Hex^n, $HOMe_2C$, $CH_2{=}CHCH_2(CO_2Et)_2CCH_2$, Ph

Scheme 320



R^1 = H, *n*-$C_{10}H_{21}$, $HOCH_2$
R^2 = H, Me
R^1-R^2 = $(CH_2)_4$, $(CH_2)_5$

Scheme 321

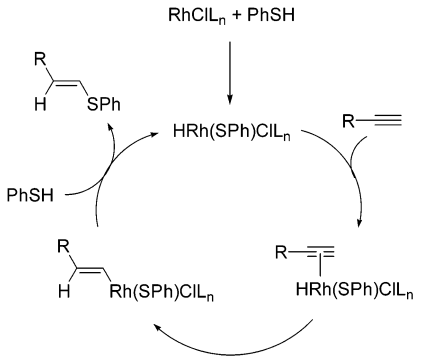


$Pd(OAc)_2$ catalysis led to the predominant formation of the Markovnikov products (Scheme 319) with variable amounts of secondary products derived from their carbon−carbon double bond isomerization or the double addition of PhSeH to the alkyne. However, phenylacetylene led to a mixture of regioisomers because of the competitive palladium-catalyzed and free-radical addition processes. Trying to elucidate the stereochemistry of formation of the Markovnikov product, the authors carried out the $Pd(OAc)_2$-catalyzed reaction of 1-octyne and PhSeD, thus demonstrating that at least a 80% of the reaction proceeds as *syn*-addition. A similar reaction mechanism to that depicted in Scheme 318 was proposed in which, taking into consideration that the acidity of PhSeH is only slightly higher than that of PhSH, the reductive elimination from the corresponding vinylpalladium intermediate also could be expected to compete with protonolysis (see the previous paragraph). In fact, a palladium-catalyzed reaction of PhSeSePh and RC≡CH to form $R(PhSe)C{=}C(SePh)H$ has been recently published.[420]

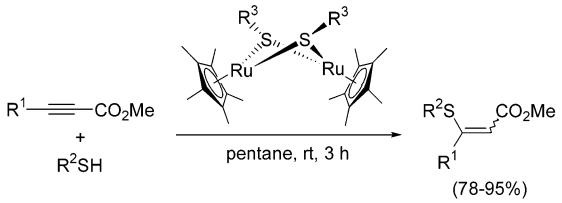
The methodology settled by Ogawa, Sonoda et al. was applied by Bäckvall et al. to the addition of thiophenol to conjugated enynes with a terminal carbon−carbon triple bond.[421] The reaction was chemo- and regioselective, affecting only to the carbon−carbon triple bond in an Markovnikov fashion to produce 2-(phenylthio) 1,3-dienes (Scheme 320). Unfortunately, the reaction of enynes with an internal carbon−carbon triple bond failed under these reaction conditions.

Ogawa, Hirao et al. discovered the ability of $Pd(PhCN)_2Cl_2$ to catalyze the Markovnikov addition of thiols to terminal alkynes bearing propargylic hydrogens, followed by isomerization of the carbon−carbon double bond, thus providing internal vinylic sulfides regioselectively but as a ca. 1:1 mixture of diastereoisomers (Scheme 321).[422] In contrast, Wilkinson's catalyst, $Rh(PPh_3)_3Cl$, exhibited a complementary behavior, affording the corresponding anti-

Scheme 322



Scheme 323



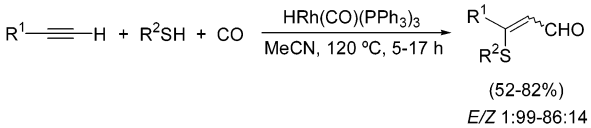
R^1 = H, CO$_2$Me
R^2 = Et, Pr^i, Bu^t, Bn, Ph, C$_6$F$_5$
R^3 = Et, Pr^i, Bu^t

Markovnikov vinylic sulfides regioselectively and with exclusive formation of the (*E*)-diastereoisomers (Scheme 321). In the latter reaction, not only PhSH but also *p*-ClC$_6$H$_4$SH and *p*-MeOC$_6$H$_4$SH gave good results. The suggested catalytic cycle for the Rh(PPh$_3$)$_3$Cl-catalyzed hydrothiolation includes (a) the oxidative addition of PhSH to Rh(I), (b) activation of the carbon−carbon triple bond by the resulting hydrido complex, (c) stereoselective *syn*-insertion of the alkyne into the Rh−H bond (the regiochemistry of this type of insertion is probably controlled by both steric and electronic factors), and (d) final reductive elimination (Scheme 322).

Binuclear ruthenium complexes of the type Cp*Ru(μ-SR)$_2$RuCp* (R = Et, Pr^i, Bu^t) and Cp*Ru(η^1-C$_6$F$_5$)(μ-S)(μ-SC$_6$F$_5$)$_2$RuCp* were found to be active catalysts for the addition of thiols to polar alkynes at room temperature (Scheme 323).[423] Thus, methyl propiolate reacted regioselectively, giving the anti-Markovnikov vinyl sulfide, whereas DMAD led to a mixture of diastereoisomers in which the (*Z*)-isomer prevailed. A mechanism for the catalytic cycle was proposed based on the isolation and characterization of some intermediate complexes, including vinylidene complexes.

The vinylic metal complexes that take part as intermediates in the transition-metal-catalyzed hydrothiolation or hydroselenation of alkynes can be trapped with carbon monoxide to produce the products of thioformylation or selenoformylation, respectively. This topic was pioneered by Ogawa, Sonoda et al. with the finding that the carbonylative addition of diaryl disulfides and diselenides to terminal acetylenes catalyzed by Pd(PPh$_3$)$_4$ led to the regio- and stereoselective formation of (*Z*)-1,3-bis(arylthio)- and (*Z*)-1,3-bis(arylseleno)-2-alken-1-ones, respectively.[412a,418a,424] With these antecedents, this group found that rhodium(I) complexes bearing phosphine ligands exhibited excellent catalytic activity in the thioformylation of acetylenes.[425] The best results were obtained with the action of HRh(CO)(PPh$_3$)$_3$ over aliphatic or aromatic terminal acetylenes with arenethiols, alkanethiols requiring prolonged reaction times (Scheme 324).

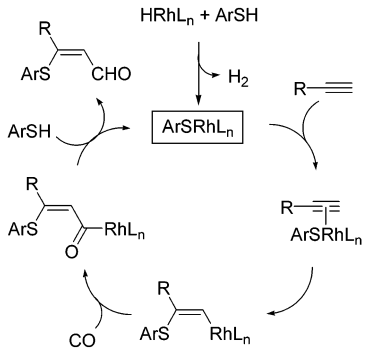
Scheme 324



E/*Z* 1:99-86:14

R^1 = Hex^n, Pent^i, Ph, HO(CH$_2$)$_3$, Bn, NC(CH$_2$)$_3$, HC≡C(CH$_2$)$_4$
R^2 = Ph, *p*-FC$_6$H$_4$, *p*-MeC$_6$H$_4$, *n*-C$_{12}$H$_{25}$

Scheme 325



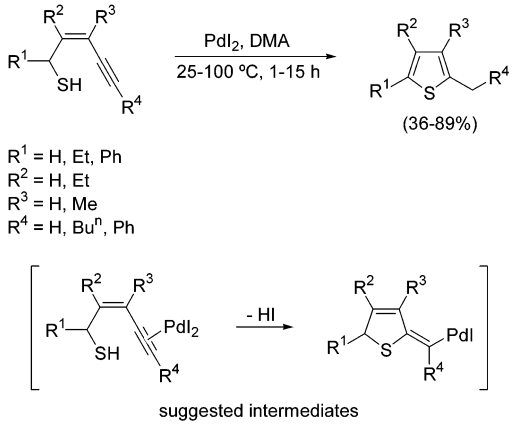
For the above reaction, the authors suggested a catalytic cycle (Scheme 325) with the participation of ArSRh(CO)(PPh$_3$)$_2$, the formation of which was demonstrated by reacting HRh(CO)(PPh$_3$)$_3$ with PhSH. It should be pointed out that in this case, insertion of the alkyne into the Rh−S bond resulted in opposite regioselectivity in comparison with the rhodium-catalyzed hydrothiolation (see Scheme 322). The formation of the formyl group could be explained by oxidative addition of ArSH to the intermediate acyl complex, generating a hydrido−rhodium complex R(ArS)C=CHCORhH(SAr)(L$_n$), followed by reductive elimination. A competitive reductive elimination pathway would account for the obtention of equal amounts of the thioformylation product and thioester in the reaction with the aliphatic thiol.

By switching the catalyst from HRh(CO)(PPh$_3$)$_3$ to Pt(PPh$_3$)$_4$, a dramatic reversal of regioselectivity in the introduction of CO was observed. This novel thiocarbonylation, with a hydride and a thiocarbonyl group being introduced into the terminal and internal positions of the alkynes, respectively, led to the corresponding α,β-unsaturated thioesters CH$_2$=C(R)-COSPh in good to excellent yields.[426] This methodology has been exploited by others using palladium complexes.[427] Nonetheless, this topic will not be covered herein since no vinylic sulfide moiety formation is involved in this reaction.

7.2. Intramolecular Processes

To the best of our knowledge, the only example of intramolecular transition-metal-catalyzed hydrothiolation of alkynes was reported by Gabriele, Salerno et al.[428] The authors synthesized a series of substituted thiophenes by the palladium-catalyzed cycloi-

Scheme 326



somerization of (*Z*)-2-en-4-yne-1-thiols, using PdI_2 as catalyst under relatively mild reaction conditions (Scheme 326). Enynethiols bearing a terminal carbon−carbon triple bond were more reactive than those substituted at C-5, substitution at C-3 also retarding the reaction course. This behavior was in agreement with a mechanism involving electrophilic activation of the carbon−carbon triple bond, followed by intramolecular nucleophilic attack, protonolysis, and final aromatization.

8. Hydrophosphination, Hydrophosphinylation, and Hydrophosphorylation

This section covers the formation of phosphorus−carbon bonds by the metal-catalyzed addition of phosphorus−hydrogen bonds present in P(III) reagents (hydrophosphination) and P(V) reagents (hydrophosphinylation and hydrophosphorylation) to alkynes.

Alkenylphosphines are attracting current interest as useful ligands to activate various substrates within their transition-metal complexes[429] and as precursors of a variety of functional ligands by modification of their carbon−carbon double bond including enantioselective catalysis.[430] On the other hand, the intramolecular version of this reaction leads to phosphorus heterocycles that belong to a class of interesting alkaloid mimics[431] and act as ligand building blocks in asymmetric catalysis.[432] The uncatalyzed preparation of vinylphosphines by phosphine addition to alkynes has been accomplished in superbasic media[433] or under radical conditions,[434] in many cases requiring a properly activated alkyne.[435]

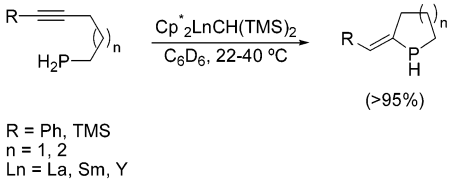
Alkenylphosphine oxides also possess a wide spectrum of applications either as biologically active compounds,[436] fire retardants,[437] or ligands for homogeneous catalysis[438] and asymmetric synthesis.[439] However, noncatalyzed synthetic methods available are quite limited.[440] Alkenylphosphonates, which are not readily accessible by conventional methods, are both synthetically versatile and biologically active.[441]

In general, when the above-mentioned type of compounds are prepared under transition-metal catalysis, notable improvements in rate and regio- and stereoselectivity are observed.[44e,442]

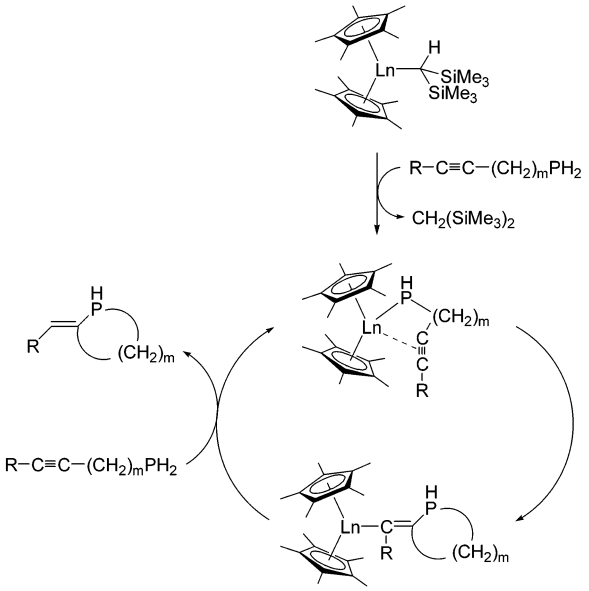
8.1. Hydrophosphination

The metal-catalyzed hydrophosphination of alkynes has been little explored, only a few examples of

Scheme 327



Scheme 328

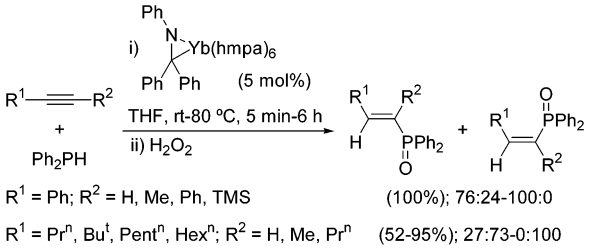


intramolecular processes with organolanthanide complexes having been reported, together with some palladium-, rhodium-, and nickel-catalyzed intermolecular reactions.

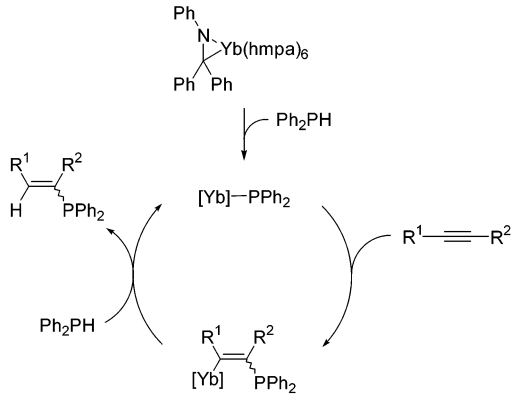
Marks et al. described the first catalytic intramolecular hydrophosphination−cyclization of primary phosphinoalkynes using the same organolanthanide precatalysts used for hydroamination reactions. Thus, complexes of the type $Cp^*_2LnCH(TMS)_2$ (Ln = La, Sm, Y) and $Me_2Si(Me_4C_5)(Bu^tN)SmN(TMS)_2$ proved to be active precatalysts for the above-mentioned reaction, producing the corresponding secondary phospholanes with very high conversion under mild reaction conditions (Scheme 327).[46,443] Unfortunately, the cyclization products were somewhat unstable and could only be characterized in situ by NMR. It was observed that the reaction rate increased with increasing Ln^{3+} ionic radius (opposite to the behavior observed for aminoalkynes) as well as in the presence of more open supporting ligand systems in the precatalyst. The catalytic cycle suggested includes the insertion of the carbon−carbon triple bond into the Ln−P bond as the rate-determining step, followed by rapid Ln−C protonolysis to afford the product heterocycle and regenerate the metal−heteroatom bond (Scheme 328).

The intermolecular hydrophosphination of terminal and internal alkynes with Ph_2PH was successfully performed by Takaki et al. in a regio- and stereoselective manner using a ytterbium−imine complex, $Yb(\eta^2\text{-}Ph_2CNPh)(hmpa)_6$, prepared in situ from Yb metal and the aromatic imine.[444] Reactions proceeded extremely fast under mild reaction conditions for alkynes bearing phenyl groups, the expected alkenyl

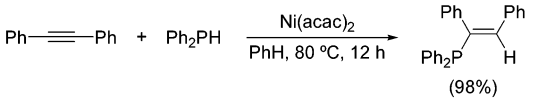
Scheme 329



Scheme 330



Scheme 331

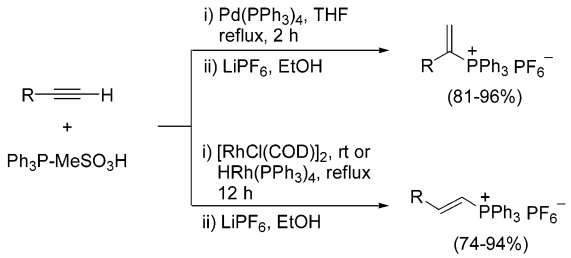


phosphine oxides being quantitatively obtained after oxidative workup (Scheme 329). For aromatic alkynes the Ph_2P group was exclusively introduced at the opposite side of the aryl substituent with preferential *E* stereochemistry. In contrast, for aliphatic alkynes the regioselectivity was not so high and the stereochemistry was mainly *Z*. From a mechanistic point of view, the formation of a catalytic phosphide intermediate [Yb]−PPh_2, insertion of the alkyne into the Yb−P bond, and regeneration of the catalyst by protonolysis with Ph_2PH was suggested (Scheme 330).

Beletskaya et al. described a new approach to the synthesis of vinyl phosphines based on the palladium- and nickel-catalyzed addition of diphenylphosphine to terminal and internal alkynes.[445] In general, nickel complexes were found to be more efficient than palladium complexes as catalysts, the regio- and stereoselectivity of the reaction with terminal alkynes strongly depending on the nature of the alkyne, catalyst, and reaction conditions. On the other hand, the addition reaction of Ph_2PH to tolane catalyzed by $Ni(acac)_2$ led to (*E*)-diphenyl(1,2-diphenylvinyl)-phosphine in very good yield and high stereoselectivity as a result of a *syn*-addition (Scheme 331).

An unprecedented transition-metal-catalyzed addition reaction of a tertiary phosphine to unactivated alkynes was discovered by Yamaguchi et al.[446] Thus, under the action of $Pd(PPh_3)_4$ and in the presence of methanesulfonic acid, triphenylphosphine attacked the internal carbon atom of a variety of terminal alkynes regioselectively (Markovnikov addition), affording the corresponding vinyl phosphonium salts

Scheme 332



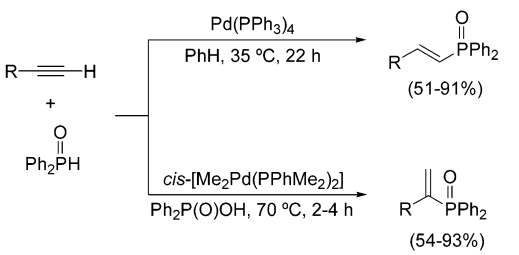
in high yields (Scheme 332). Under these reaction conditions, alcohol, ester, and nitrile functionalities remained unaffected, albeit other tertiary phosphines such as diphenylmethylphosphine and tri-*n*-butylphosphine were inert. The internal acetylene 4-octyne also reacted giving the (*E*)-isomer, whereas double addition was observed for the substrate 1,4-bis(trimethylsilyl)-1,3-butadiyne. It is worth noting that in the presence of a rhodium catalyst, the observed regioselectivity was opposite to that of the palladium-catalyzed reaction (anti-Markovnikov mode) (Scheme 332).

8.2. Hydrophosphinylation

Tanaka et al. reported the first efficient palladium-catalyzed regio- and stereoselective hydrophosphinylation of terminal alkynes to furnish the corresponding alkenylphosphine oxides.[447] Reactions were performed with $Pd(PPh_3)_4$ as catalyst under mild reaction conditions, providing the anti-Markovnikov products with *E* stereochemistry (Scheme 333). A wide variety of alkynes including acetylene, alkyl, aryl, and functionalized alkynes as well as diynes and internal alkynes were also successfully hydrophosphinylated. Surprisingly, the regioselectivity of this reaction was completely reversed by the addition of a trace amount of diphenylphosphinic acid in the presence of *cis*-$[Me_2Pd(PPhMe_2)_2]$ (Scheme 333).[448] In this case, the authors suggested a reaction pathway involving the generation of new palladium species, followed by insertion of the alkyne into the Pd−P(O)-Ph_2 bond (phosphinylpalladation), and subsequent protonolysis with $Ph_2P(O)H$ (Scheme 334). However, several questions remain unclear, such as how the new palladium species arises from the starting palladium catalyst and the fact that the protonolysis is effected by $Ph_2P(O)H$ in the presence of $Ph_2P(O)OH$.

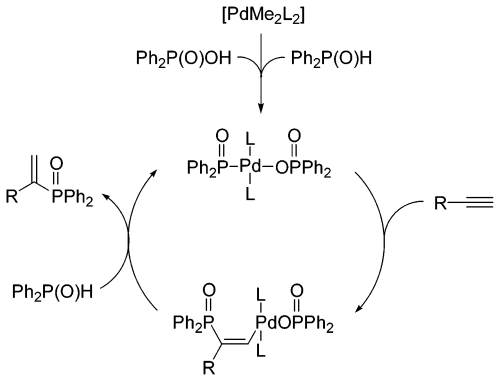
Addition of diphenylphosphine oxide to a variety of alkynes was also accomplished with the rhodium catalyst $Rh(PPh_3)_3Br$, which allowed the preparation of (*E*)-alkenylphosphine oxides in a regio- and ste-

Scheme 333

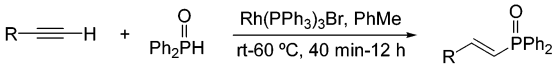


R = H, Hexn, Ph, *p*-MeC_6H_4, $NC(CH_2)_3$, $HO(CH_2)_2$, cyclohex-1-enyl

Scheme 334

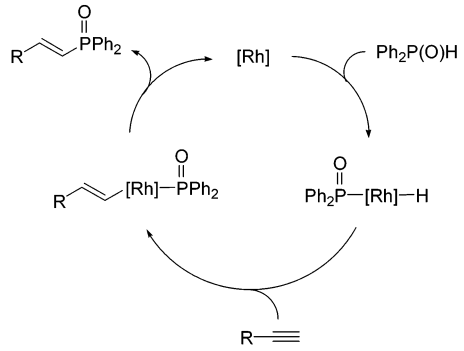


Scheme 335

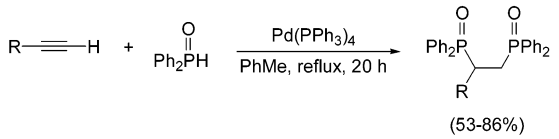


R = H, Bu^t, Hex^n, Ph, NC(CH$_2$)$_3$, HO(CH$_2$)$_2$, Cl(CH$_2$)$_3$, Bu^{t}CO$_2$(CH$_2$)$_2$, Bu^n$_2$NCH$_2$, TMS, TMSCH$_2$, 2-thienyl, ferrocenyl, cyclohex-1-enyl

Scheme 336



Scheme 337

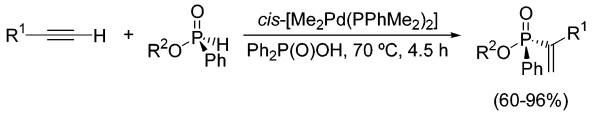


R = Pent^n, Cy, Ph, *p*-XC$_6$H$_4$ (X = NMe$_2$, CN, NO$_2$), 2-pyridyl, 4-pyridyl, 5-nitro-2-pyridyl, 2-thiazolyl

reoselective manner under mild reaction conditions (Scheme 335).[449] Both aliphatic and aromatic terminal alkynes bearing diverse functionalities as well as an internal alkyne and a diyne reacted efficiently under these conditions. A tentative mechanistic proposal included the oxidative addition of the P−H bond of diphenylphosphine oxide to rhodium, followed by alkyne insertion into the Rh−H bond, and reductive elimination (Scheme 336).

Lin et al. studied the palladium-catalyzed bishydrophosphinylation reaction of terminal alkynes and diphenylphosphine oxide to give bisphosphine oxides that could be easily reduced to their corresponding bisphosphines.[450] The reaction was applied to various aliphatic and aromatic terminal alkynes bearing electronically neutral, electron-withdrawing, and electron-donating functionalities (Scheme 337). A similar mechanism to that depicted in Scheme 336 was suggested in which the resulting alkenyl diphenylphosphine oxide underwent a second hydrophosphinylation.

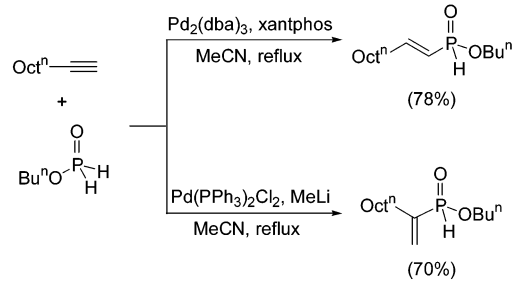
Scheme 338



R^1 = H, Hex^n, NC(CH$_2$)$_3$, Cl(CH$_2$)$_3$, Bu^{t}CO$_2$(CH$_2$)$_2$, TMS, cyclohex-1-enyl ferrocenyl, Ph, 2,4,6-Me$_3$C$_6$H$_2$, *p*-MeOC$_6$H$_4$, *p*-ClC$_6$H$_4$

R^2 = (-)-menthyl

Scheme 339



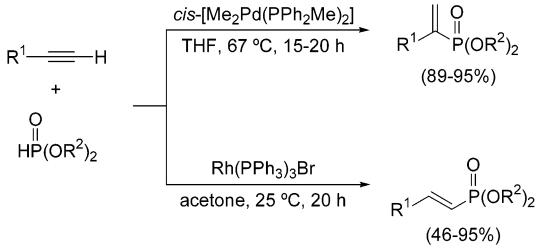
The previously commented catalytic system developed by Tanaka et al., *cis*-[Me$_2$Pd(PPhMe$_2$)$_2$]−Ph$_2$P(O)OH (see Scheme 333), was also effective for the addition of chiral phenylphosphinates to a wide range of alkynes.[451] The reaction proceeded with >95% Markovnikov regioselectivity and with retention of the configuration at phosphorus. Thus, starting from acetylene, alkyl, aryl, and functionalized alkynes as well as diynes and internal alkynes, the corresponding enantiomerically pure (R_P)-vinylphosphinates were obtained in high yields (Scheme 338).

Recently, Montchamp et al. developed a palladium-catalyzed hydrophosphinylation reaction of alkynes with hypophosphorus compounds of the type ROP(O)H$_2$ (R = H, alkyl, Ph) to form vinyl phosphinates.[452] Terminal alkynes gave the branched vinylphosphinate exclusively with catalytic Pd(PPh$_3$)$_2$Cl$_2$−MeLi, whereas the linear product was the major component with Pd$_2$(dba)$_3$−xantphos (Scheme 339.)

8.3. Hydrophosphorylation

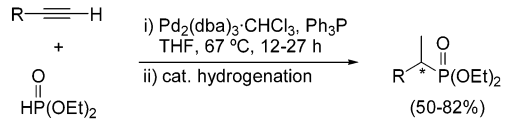
During recent years Tanaka et al. investigated the transition-metal-catalyzed hydrophosphorylation of alkynes to obtain alkenylphosphonates. This group discovered the important role played by the nature of the catalyst to control the regioselectivity of the reaction. Thus, within the palladium catalysts, *cis*-Me$_2$Pd(PPh$_2$Me)$_2$ exhibited the best results in the addition of dimethyl phosphite to both aliphatic and aromatic terminal alkynes, providing the corresponding Markovnikov alkenylphosphonates in high yield and regioselectivity (Scheme 340).[453] Two phosphoryl groups were easily introduced in diynes, carbon−carbon double bonds being totally unreactive. For bulky trimethylsilylacetylene, opposite regioselectivity was observed, whereas the hydrophosphorylation of internal alkynes proceeded slower. On the other hand, by using Wilkinson-type complexes as catalysts, Rh(PPh$_3$)$_3$X, the hydrophosphorylation of terminal alkynes led to the highly selective formation of (*E*)-alkenylphosphonates with complete reversal of

Scheme 340



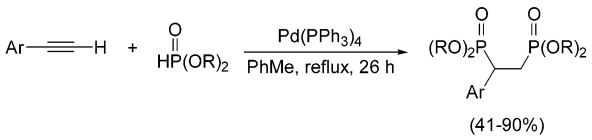
R^1 = H, alkyl, functionalized alkyl, aryl
R^2 = Me, for the palladium-catalyzed reaction
$(OR^2)_2$ = $OCMe_2CMe_2O$, for the rhodium-catalyzed reaction

Scheme 341



R = Bu^n, Bu^t, Ph, *p*-$MeOC_6H_4$, 1-naphthyl, 6-MeO-2-naphthyl, ferrocenyl, 3-pyridyl, 3-quinolyl, 5-quinolyl

Scheme 342



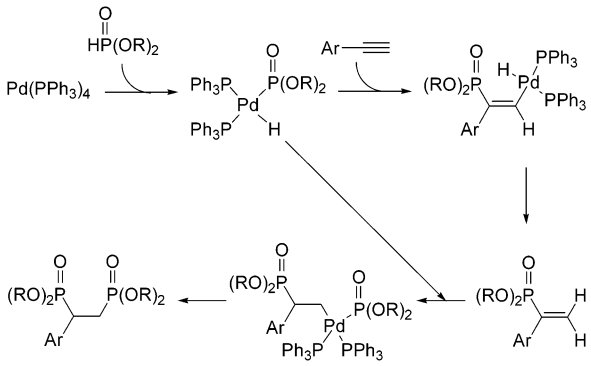
Ar = *p*-$NO_2C_6H_4$, *p*-NCC_6H_4, 2-pyridyl, 4-pyridyl, 2-thiazolyl
R = Et, Pr^i

regioselectivity (anti-Markovnikov) to the palladium-catalyzed counterpart.[454] Reactions proceeded at room temperature and were applicable to a wide variety of terminal alkynes bearing diverse kinds of functionalities (Scheme 340). Both metal-catalyzed reactions were suggested to take place via insertion of the alkyne into a $(RO)_2P(O)-[M]-H$ species.

Tanaka's procedure involving the palladium-catalyzed hydrophosphorylation of terminal alkynes was modified by Beletskaya, Genêt et al. introducing commercially available $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of Ph_3P instead of using the air-sensitive $Pd(PPh_3)_4$ or *cis*-$Me_2Pd(PPh_2Me)_2$ complexes. A variety of diethyl alkyl-, aryl-, and heteroarylvinylphosphonates were synthesized as a result of the Markovnikov addition, which upon hydrogenation (including asymmetric hydrogenation) gave a series of biologically active compounds with a phosphorus analogue of naproxen among them (Scheme 341).[455]

Finally, Lin et al. applied the same palladium-based catalytic system used for the bis-hydrophosphinylation of terminal alkynes (see Scheme 337) to the synthesis of functionalized bisphosphonates by the bis-hydrophosphorylation reaction of electron-deficient terminal alkynes and dialkyl phosphites (Scheme 342).[456] Better results were obtained for diethyl phosphite in comparison with diisopropyl phosphite, whereas either with dimethyl phosphite in the absence of electron-withdrawing functionalities on the aryl groups or using 1 equiv of dialkyl phosphite the predominant monohydrophosphorylation led to the Markovnikov alkenyl phosphonates. The palladium hydride $HPd(PPh_3)_2P(O)(OR)_2$ was proposed to be the active catalyst, which by alkyne

Scheme 343



insertion into the Pd−P bond followed by reductive elimination would generate an intermediate alkenyl phosphonate. The latter would undergo a second hydrophosphorylation reaction, through insertion into the Pd−H bond of the active catalyst, followed by final reductive elimination (Scheme 343).

9. Conclusions

The addition reaction of Het−H bonds (Het = N, O, S, Se, P) to alkynes is of paramount value since it allows the straightforward preparation of a wide variety of functionalized unsaturated compounds of enormous interest. These compounds have found diverse applications in industry, as intermediates in synthetic organic chemistry, or in medicinal chemistry due to the important properties that they have as a result of their biological activity. Another interesting advantage of this reaction is its high atom efficiency, which simplifies the reaction mixture and therefore minimizes the economic cost of the process.

Despite the different noncatalytic procedures appearing in the literature to effect the title reaction, the transition-metal-catalyzed methodologies represent the best choice because of their high efficiency, generally involving milder reaction conditions and exhibiting higher selectivities. The former reaction systems to perform these transformations were primarily based on the use of mercury(II) compounds, which with the advent of the modern organometallic chemistry were progressively substituted by the more environmentally friendly transition-metal complexes.

The design and/or choice of the appropriate transition-metal catalyst is conditioned by the multiple parameters involved in the addition reaction. Thus, regarding the substrates, we must take into account whether we are dealing with an inter- or intramolecular process since, in general, intermolecular additions are more difficult than the intramolecular counterparts. The structure of the alkyne is also important, terminal and internal alkynes often behaving differently and depending on the substitution pattern, i.e., the presence or absence of bulky substituents, electron-withdrawing, electron-donating, or electronically neutral substituents. For instance, phenylacetylene is prone to undergo oligomerization products under the action of transition-metal catalysts. The nature, in particular the acidity of the Het−H bond, also plays an important role either through its transition-metal-induced activation or taking part in other steps of the catalytic cycle.

Concerning the catalyst itself, the Lewis acidity of the metal is crucial for its catalytic activity, especially in those reactions that proceed through the activation of the carbon−carbon triple bond by coordination to the metal. The type and size of the metal as well as the nature of the ligand (e.g., monodentate or bidentate, acidic or nonacidic, etc.) may exert such an influence on the course of the reaction that it can completely reverse its regioselectivity. Even the same metal in different oxidation states shows different behavior due to the various activation pathways in which it is involved [e.g., M^{2+} activation of the carbon−carbon triple bond and M(0) activation of the Het−H bond]. The performance of the catalyst can also vary depending on its whole nature (e.g., homogeneous, heterogeneous, polymer-supported, etc.).

Among all the addition reactions presented in this review, hydroamination has been the most studied one, primarily the intramolecular version. Within the early-transition-metal catalysts, the Cp-containing titanium complexes were shown to be the best precatalysts, their imido titanium species being the active catalysts. Cp_2TiMe_2 has been the most utilized for both inter- and intramolecular reactions, mainly involving internal alkynes and preferentially leading to the Markovnikov products. Lanthanide and actinide Cp-containing catalysts can complement each other since, for instance, $Cp^*_2LnCH(TMS)_2$ found application above all in intramolecular processes whereas $Cp^*_2AnMe_2$ only worked for the intermolecular hydroamination of terminal alkynes. Within the early-transition-metal catalysts, $Ru_3(CO)_{12}$ was especially active in the intermolecular hydroamination of terminal alkynes with aromatic amines through activation of the N−H bond. We must highlight that palladium is the most studied and versatile metal in hydroamination processes, allowing the intramolecular addition of amines to alkynes bearing different functionalities and leading to a wide variety of very interesting nitrogenated heterocycles such as cyclic imines, pyrroles, dihydropyrroles, lactams, oxazolidinones, pyrazoles, pyridines, dihydropyridines, indoles, quinolones, azaindoles, isoindolines, isoindolinones, isoquinolines, dihydro- and tetrahydroisoquinolines, or carbolines, among others. The synthesis of substituted indoles using this methodology has attracted the attention of many research groups, the intermediate vinylpalladium species allowing further reaction with organic (vinyl and aryl) halides or triflates, α,β-unsaturated compounds, alkoxycarbonylation reactions, or Heck reactions with electron-deficient alkenes. The palladium-catalyzed intramolecular hydroamination methodology has been successfully extended to the synthesis of naturally occurring compounds.

Regarding the hydroalkoxylation of alkynes, a variety of oxygen-containing heterocycles have been prepared by the cycloisomerization of terminal alkynyl alcohols under molybdenum, tungsten, and ruthenium catalysts through their metal vinylidene complexes. Most of the research on this topic has focused on the use of palladium catalysts applied to intramolecular processes and leading to furans, dihydro- and tetrahydrofurans, pyrans, dihydro- and tetrahydropyrans, benzofurans, flavones, chromones, etc. Different methodologies involving the cyclization, cyclization−coupling, or cyclization−alkoxycarbonylation of *o*-alkynylphenols as well as the coupling−cyclization of *o*-iodophenols and alkynes have allowed the preparation of differently substituted benzofurans. However, other metals such as copper, silver, gold, zinc, and mercury were of more limited application.

Ruthenium and palladium catalysts complement each other in the hydro-oxycarbonylation of alkynes. Thus, ruthenium complexes have been utilized as effective precatalysts for intermolecular processes. They have been shown to be particularly useful for the hydro-oxycarbonylation of terminal alkynes with Markovnikov regioselectivity as well as for the synthesis of vinyl carbamates from terminal alkynes, carbon dioxide, and dialkylamines. Ruthenium vinylidene intermediates are mainly involved in these reactions. On the other hand, palladium catalysts exhibited better behavior in intramolecular additions, furnishing a variety of lactones of different size, butenolides, isocoumarins, phthalides, or pyranones. It is worth noting that silver salts were also effective catalysts for intramolecular hydro-oxycarbonylation reactions and superior to palladium in some cases. Mercury(II) compounds, formerly used as efficient catalysts in the intramolecular processes, are nowadays of more restricted use for all known reasons.

At one time, mercury(II) compounds also played an important role in catalyzing the hydration of alkynes, especially the hydration of acetylene to give acetaldehyde. Nowadays, ruthenium catalysts are most commonly used, above all for the hydration of terminal alkynes. The regioselectivity of the reaction can be easily controlled by choosing the appropriate ruthenium catalyst. Rhodium and platinum halides as well as some palladium, iridium, copper, and gold compounds also found application in some particular cases.

The hydrothiolation and hydroselenation of alkynes has been studied little and dedicated mainly to intermolecular processes with Markovnikov addition to terminal alkynes under ruthenium, rhodium, and palladium catalysis. Lanthanide catalysts proved to be efficient in the intramolecular hydrophosphination of alkynes, whereas rhodium, palladium, and nickel catalysts found better application in intermolecular processes. The hydrophosphinylation and hydrophosphorylation reactions are mainly applied to terminal alkynes and mainly accomplished with palladium catalysts. It is worth noting the easy control of the regiochemistry in the preparation of alkenylphosphorus compounds by selecting the appropriate catalyst.

We believe that the topic of this review will be important during the coming years, with a high production of new results, due to the potential of these reactions and fact that many aspects remain unclear. For instance, in many cases it is difficult to elucidate the real mechanism that controls the regio- and stereoselectivity of the reaction. On the other hand, the less favored intermolecular addition pro-

cesses would also deserve further attention and study.

10. Abbreviations

acac	acetylacetonate
Ala	alanine
Alloc	allyloxycarbonyl
An	actinide
Asp	aspartic acid
ATI	aminotroponiminate
Boc	*tert*-butoxycarbonyl
BEA	zeolite beta
Bz	benzoyl
cat.	catalytic
Cbz	benzyloxycarbonyl
COD	1,5-cyclooctadiene
cod	cyclooctadienyl
COT	1,3,5-cyclooctatriene
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
CTAB	hexadecyltrimethylammonium bromide
Cy	cyclohexyl
cycphos	1,2-bis(dicyclohexylphosphino)ethane
dap	α-(dimethylaminomethyl)pyrrole
dba	dibenzylideneacetone
DMA	*N*,*N*-dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DME	1,2-dimethoxyethane
DIPAMP	1,2-bis[(*o*-methoxyphenyl)(phenyl)phosphino]-ethane
DIPEA	diisopropylethylamine
dmfm	dimethyl fumarate
dpma	*N*,*N*-di(pyrrolyl-α-methyl)methylamine
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppm	bis(diphenylphosphino)methane
dppp	1,3-bis(diphenylphosphino)propane
dppt	1,5-bis(diphenylphosphino)pentane
EDTA	ethylenediaminetetraacetic acid
equiv	equivalent
Gly	glycine
$HB(pz)_3$	tris(pyrazolyl)borate
Hep	heptyl
Het	heteroatom
Hex	hexyl
hmpa	hexamethylphosphoramide
Ind	indenyl
L	ligand
Ln	lanthanide
M	metal
MEM	methoxymethyl
mim	*N*-methylimidazol-2-yl
Ms	methanesulfonyl
MOM	methoxymethyl
MVK	methyl vinyl ketone
MW	microwaves
NBD	norbornadiene
NHS	*N*-hydroxysuccinimide
Nu	nucleophile
Oct	octyl
Pent	pentyl
Phe	phenylalanine
phen	1,10-phenantroline
Piv	pivaloyl
PNIPAM	poly(*N*-isopropylacrylamide)
Pro	proline
PS	polystyrene
PTC	phase-transfer conditions
Py	pyridine
rt	room temperature
SDS	sodium dodecyl sulfate
tacn	1,4,7-triazacyclononane
TBAB	tetra-*n*-butylammonium bromide
TBAC	tetra-*n*-butylammonium chloride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEBA	benzyltriethylammonium chloride
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMG	tetramethylguanidine
TMNO	trimethylamine *N*-oxide
TMS	trimethylsilyl
TMSE	2-(trimethylsilyl)ethyl
TOF	turnover frequency (mol of product per mol of catalyst h^{-1})
Tol	tolyl
TON	turnover number (mol of product per mol of catalyst)
TPPTS	tris(sodium *m*-benzenesulfonate)phosphine
Triphos	bis(diphenylphosphinoethyl)phenylphosphine
Ts	*p*-toluenesulfonyl
ttmpp	tris(2,4,6-trimethoxyphenyl)phosphine
xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

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