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Valentine P. Ananikov
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Hydrofunctionalization

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Aims and Scope

The series *Topics in Organometallic Chemistry* presents critical overviews of research results in organometallic chemistry. As our understanding of organometallic structures, properties and mechanisms grows, new paths are opened for the design of organometallic compounds and reactions tailored to the needs of such diverse areas as organic synthesis, medical research, biology and materials science. Thus the scope of coverage includes a broad range of topics of pure and applied organometallic chemistry, where new breakthroughs are being made that are of significance to a larger scientific audience.

The individual volumes of *Topics in Organometallic Chemistry* are thematic. Review articles are generally invited by the volume editors.

In references *Topics in Organometallic Chemistry* is abbreviated Top Organomet Chem and is cited as a journal. From volume 29 onwards this series is listed with ISI/Web of Knowledge and in coming years it will acquire an impact factor.

Preface

Transition metal catalysis is a major driving force for development of new approaches in organic synthesis, medicinal chemistry, preparation of biologically active and pharmaceutical molecules, as well as in numerous applications related to material science and molecular electronics. Recent advances in green and sustainable chemistry emphasized the key role of waste-free chemicals production. Especially critical in fine chemicals synthesis is that high values of E-factor are not uncommon. Increasing demand in very complex molecular structures enforces implementation of sophisticated multistep synthetic procedures and further complicates the waste/product balance. On the other hand, so far most of the commodity chemicals remain to be produced by classical procedures, which are not green.

A fundamental solution to the problem is to develop novel synthetic processes that are "clean" by initial design. For carbon–heteroatom bond formation it is the hydrofunctionalization process that opens the possibility for environmentally friendly chemical transformations. Hydrofunctionalization of unsaturated organic molecules via direct addition of H-X to multiple bonds is an atom-economical addition reaction which does not produce wastes. In view of the need of green and sustainable chemical procedures, the role of the metal catalysis is crucial to control the reaction, in particular, regio-, stereo-, and enantioselectivity.

This volume highlights fascinating development of catalytic hydrofunctionalization chemistry toward selective formation of C–X bonds (X = N, P, O, S, Se). Discovery of new catalysts, impressive development of ligands, and optimization of reaction conditions have made it possible to access molecular complexity in 100% atom-economical manner. Broad scope of the reactions, high functional group tolerance for a variety of substrates, and superior control over alternative pathways of the addition process are characteristic trends in state-of-the-art catalytic hydrofunctionalization.

The mechanistic insight into the catalytic reactions is discussed for the key insertion step [1] and catalytic hydrochalcogenation reactions [2]. Two chapters of this volume review hydroamination reaction catalyzed by early/main group [3] and late [4] metal catalysts. Synthesis of organophosphorus compounds via addition

of P–H [5] and P(O)–H [6] bonds is described next. An important area of O–H bond addition to unsaturated molecules is highlighted in three chapters depending on the nature of the metal catalyst [7–9], followed by detailed overview of synthetic pathways to organic chalcogenides [10]. Most of the hydrofunctionalization processes covered in this volume were carried out under homogeneous reaction conditions. With a noticeable exception of sulfur and selenium species, where a significant contribution of heterogeneous pathway and competing homogeneous vs. heterogeneous routes were reported. Therefore, two chapters were devoted to C–S/C–Se bonds formation focusing on mechanistic aspects [2] and outstanding synthetic potential [10].

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Yokohama, Japan — Masato Tanaka

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Alkyne and Alkene Insertion into Metal–Heteroatom and Metal–Hydrogen Bonds: The Key Stages of Hydrofunctionalization Process

Valentine P. Ananikov and Irina P. Beletskaya

Abstract In this chapter we review mechanistic concepts of carbon–heteroatom bond formation involving hydrofunctionalization of double and triple carbon–carbon bonds via migratory insertion pathway. A variety of useful synthetic procedures were developed within the scope of hydrofunctionalization reaction involving transition metal catalysts to change the direction of the addition reaction and to improve the selectivity of the process. Outstanding potential of multiple bonds activation and insertion in the metal complexes is far from being fully explored. The key factors determining insertion pathways into metal–heteroatom vs. metal–hydrogen bonds and the influence on regioselectivity of the insertion remain to be revealed in nearest future.

Keywords Alkenes · Alkynes · Catalysis · Insertion · Mechanism · Selectivity

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1 Introduction

Development of efficient and sustainable procedures for carbon–heteroatom bonds formation is the field of tremendous growth in recent decades. Discovery of new metal catalysts and preparation of new ligands contributed to a great extent to this process as a driving force in the construction of selective synthetic methods.

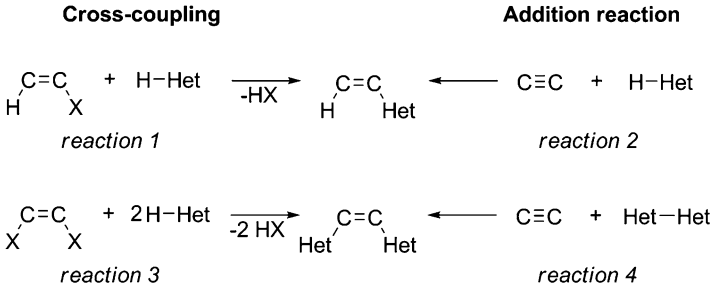
In transition-metal-catalyzed procedures carbon–heteroatom bonds can be created involving either cross-coupling or addition reactions. Representative example for the formation of C_{SP2}–Het bonds of vinyl compounds is shown in Scheme 1 (in this chapter notation Het corresponds to heteroatom or heteroatom-containing group). Cross-coupling reaction is a very powerful methodology with numerous fascinating catalytic procedures developed [1–7]. However, it is a substitution reaction and it is accompanied by the formation of by-product (i.e., HX, which is typically captured by a suitable base). In contrast, addition reaction is completely atom economic and does not suffer from by-products formation [6–13] (cf. reactions 1, 3 and 2, 4; Scheme 1).

In principle, both methodologies (cross-coupling and addition reactions) can be involved to efficiently create one or two C–Het bonds. Formation of two C–Het bonds with cross-coupling approach is a sequential process (reaction 3, Scheme 1), whereas it is a single step route in the addition reaction of Het–Het substrate to alkynes (reaction 4, Scheme 1).

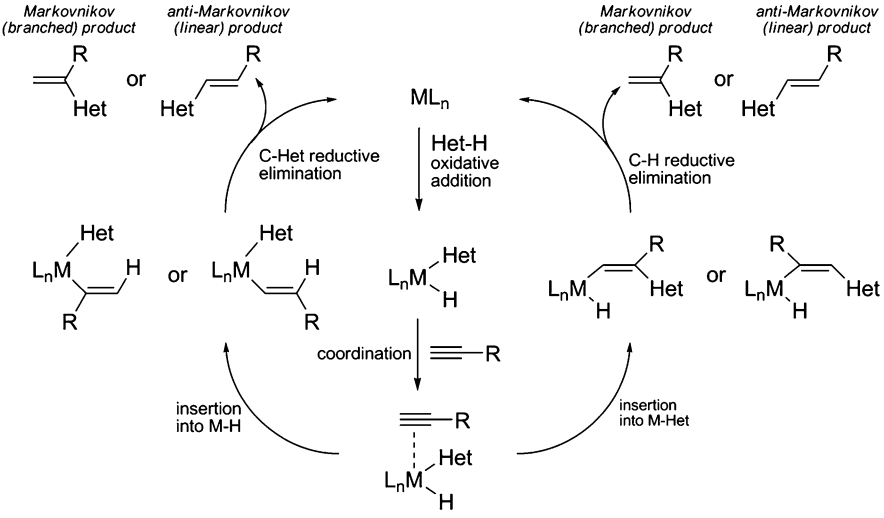
Not only intrinsic atom-economic nature but also easier availability of the carbon substrate are the important sustainable advantages of the addition reaction. Alkynes are usually commercially available, while corresponding vinyl halides may require separate synthesis.

General mechanism of H–Het addition to alkynes involves oxidative addition of H–Het to the metal center followed by multiple bond coordination and formation of the π-complex (Scheme 2). The key point of the addition reaction is the direction of alkyne insertion: insertion into the M–H or M–Het bonds and regioselectivity determine the structure of the final product – anti-Markovnikov (linear) or Markovnikov (branched). Reductive elimination of C–Het or C–H bonds is the final product releasing step in the catalytic cycle (Scheme 2).

Oxidative addition, coordination, and reductive elimination are well-known elementary steps of metal-mediated transformations [14–16]. However, insertion of multiple bonds (or migratory insertion) appears to be comparably less studied stage



Scheme 1 Cross-coupling and addition reactions in the synthesis of vinyl compounds (Het–heteroatom, X–halogen or OTf)



Scheme 2 Catalytic cycle of H–Het addition to terminal alkynes (Het–heteroatom)

with several challenging questions remaining concerning reactivity of different heteroatoms, selectivity of the reaction, and the role of ligands.

In this chapter we discuss main mechanistic problems of the key insertion step in transition-metal-catalyzed hydrofunctionalization of multiple carbon–carbon bonds. We do not make an extensive comprehensive compilation; instead, we try to focus on recent achievements and limitations in state-of-the-art understanding of the insertion reaction. Efficient utilization of hydrofunctionalization of unsaturated compounds and rational design of the catalytic procedures requires better insight into the subject and stimulates further research on this topic. Results of theoretical studies, which provided a valuable insight into the topic, are also highlighted and discussed.

2 Insertion of C=C and C≡C Bonds in the Metal Complexes

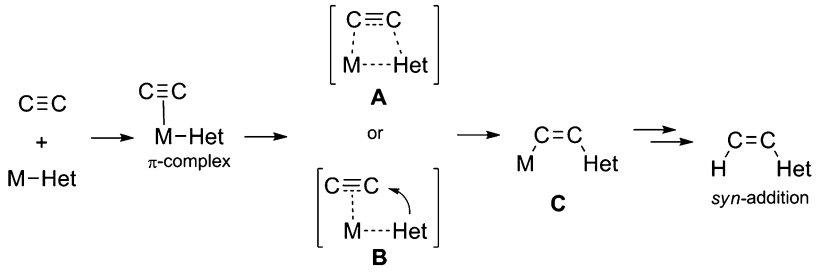
2.1 Reactions of C=C and C≡C Bonds in the Coordination Sphere of the Metal Complex

Insertion of the multiple bonds usually is considered as an inner-sphere process that takes place after binding of the Het group and after coordination of the unsaturated organic molecule. Depending on the nature of metal complex and on the type of reacting molecules, inner-sphere reaction can be depicted either as four-centered "cycloaddition-like" process (**A**, Scheme 3) or as an attack of the Het group on the coordinated multiple bond (**B**, Scheme 3). Preliminary coordination of the multiple bond in the form of π-complex is usually required to carry out inner-sphere reaction, and such coordination increases the reactivity of the unsaturated molecule (i.e., activation of C=C and C=C bonds). In both cases the same *syn*-addition product is expected and the reaction involving alkynes leads to vinyl derivatives (**C**, Scheme 3).

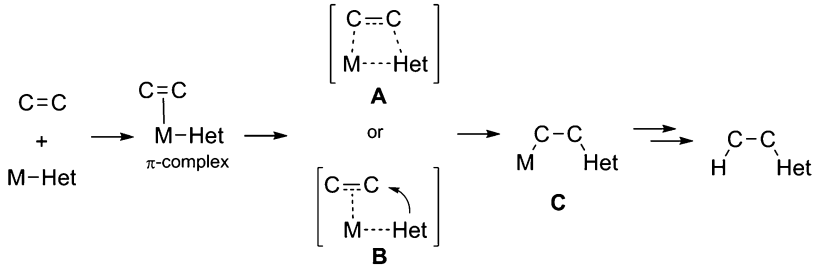
It is generally assumed that the reactions involving alkynes (Scheme 3) and alkenes (Scheme 4) proceed in the same framework. Alkene coordination followed by insertion into the M–Het bond (**A** or **B**) results in the formation of saturated compound (**C**) as a product (Scheme 4).

It should be noted that formation of *trans*-product can be achieved in an *anti*-addition reaction through the outer-sphere mechanism. Theoretical studies have demonstrated that *syn*-addition and *anti*-addition reactions may start from the same π-complex, and direction of the multiple bond activation depends on the polarity of solvent [17, 18]. Relative reactivity in the inner-sphere and outer-sphere mechanisms contributes to the overall *E-/Z-* selectivity of the addition reaction to alkynes (stereoselectivity issue). In some cases it is possible to switch the direction of C–Het bond formation by finding a suitable ligand [19]. In case of alkenes *syn*-addition and *anti*-addition processes do not necessarily result in different stereochemistry (unrestricted rotation around the single C–C bond in the product). Occurrence of these mechanisms for the N [20, 21], P [22, 23], O [24–26], S, Se [27, 28] heteroatom groups and application of different metal catalysts are discussed in detail in the other chapters of this book. Stereochemical pathways of nucleometallation and development of enantioselective catalytic procedures were reviewed [29]. In this chapter we focus our attention on the mechanism of inner-sphere insertion reaction involving double and triple carbon–carbon bonds.

The question of much interest is the difference between the transient structures **A** and **B** in the inner-sphere reactions of alkynes and alkenes (Schemes 3 and 4). On the moment it is unclear whether it is the same process just depicted in different ways or this really corresponds to a change in the mechanism depending on the nature of the reacting system. Future studies on the subject are anticipated to shed some light on this fascinating problem.



Scheme 3 Inner-sphere reaction of alkynes (Het–heteroatom)



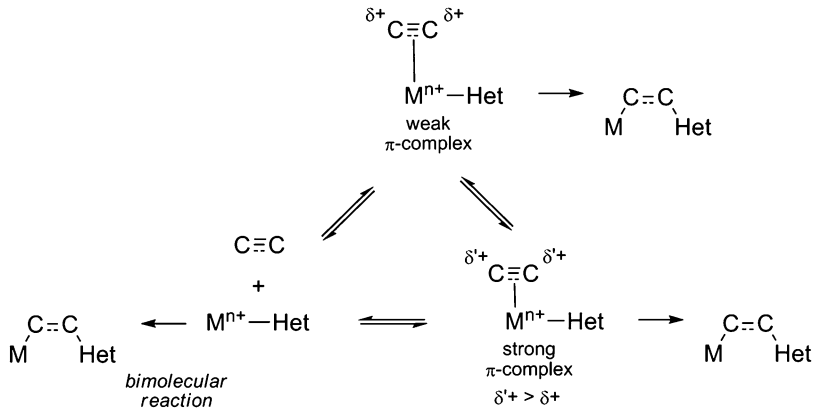
Scheme 4 Inner-sphere reaction of alkenes (Het–heteroatom)

2.2 *Preliminary Activation of the Multiple Bonds upon Coordination to the Metal*

Depending on molecular system multiple bond coordination may result in the formation of π-complexes of varying strength (Scheme 5). It is possible to distinguish boundary conditions of strong π-complex, weak π-complex, and uncoordinated system (several medium systems are also possible, but they are omitted on Scheme 5 for clarity).

Modern computational studies do provide an excellent opportunity to estimate strength of the π-complexes by calculating binding energy of the unsaturated compound [30–33]. In order to get more realistic picture of the binding process, it is important to consider not only ΔE and ΔH values, but also to analyze ΔG surface and effect of solvent. For example, weakly bound π-complex may become uncoordinated on free energy surface due to disfavoring entropy contribution and/or competitive coordination of solvent molecules.

Not only energetic data but also geometry parameters should be taken into account for correct assignment of the nature of π-complexes. The key parameters are reflected by relative changes of the length of metal–carbon bond (shorter bond for stronger π-complexes) and the length of multiple carbon–carbon bond (longer bond for stronger π-complexes). Determination of the absolute values of these bond



Scheme 5 Coordination of alkynes and alkenes to the metal center and reactivity of the π-complexes (Het–heteroatom)

lengths may require precise experiments and sophisticated computational levels; however, in most cases the relative change between coordinated and non-coordinated molecules are enough to describe the binding process. Relative changes in geometry parameters are well reproduced even at moderate computational levels [31].

As we mentioned above in Sect. 2.1, multiple bond coordination to the metal center results in activation toward the reaction with heteroatom group. In the simple approach multiple bond coordination initiates electron density redistribution and positive charge transfer from the cationic metal center to the carbon atoms (Scheme 5). Positively charged carbon atoms become more susceptible to reaction with nucleophilic center located on the heteroatom group. In this simple description stronger π-complex with larger degree of charge transfer should result in higher reactivity. Indeed, such relationship between the strength of the π-complex and exhibited reactivity was observed in several cases. However, stronger binding of the unsaturated molecule furnishes formation of the π-complex with lower relative energy and in certain cases may lead to higher activation barriers (Fig. 1). Thus, various factors have to be taken into account for selection of metal complex designed for multiple bond insertion into the M–Het bond.

In addition to energetic factors, the structure of the π-complex may play a crucial role on the performance of the catalytic reaction (Scheme 6) [34]. Alkyne insertion into the metal–sulfur bond via five-coordinated π-complex led to the formation of intermediate metal complex capable for direct C–S reductive elimination to complete product formation. In contrast, intermediate metal complex formed via alkyne insertion through the four-coordinated π-complex suffered from improper geometry configuration, which may block the whole catalytic cycle. An important issue related to reactivity of coordinated alkynes in such catalytic systems is C–Het vs. Het–Het bonds activation [35] and carbometallation vs. heterometallation pathways [36].

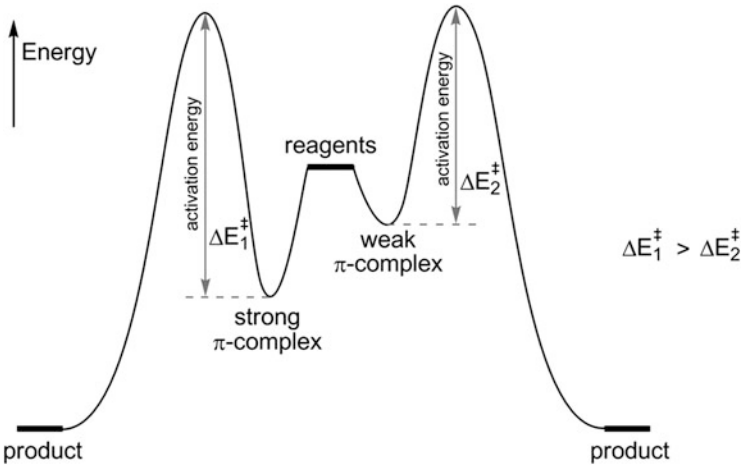
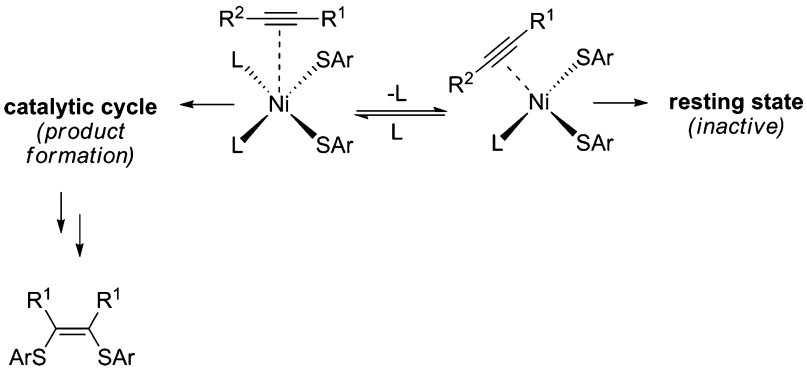
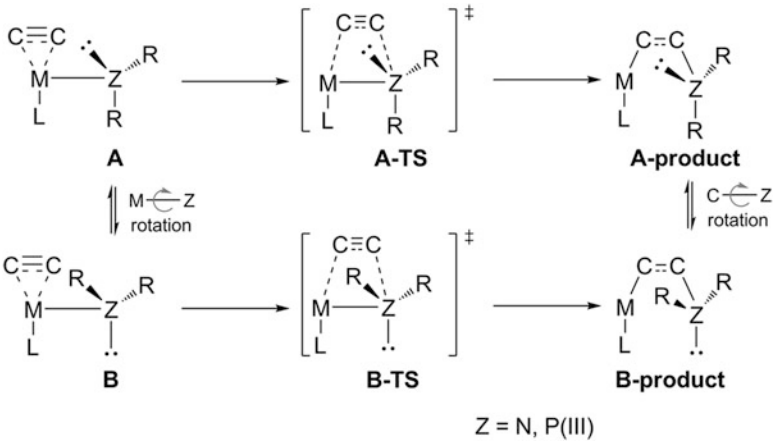


Fig. 1 Schematic representation of energy surface of insertion reaction involving strong and weak π-complex; another case with different energies of the transition states is also possible (not shown)



Scheme 6 Ni-catalyzed C–S bond formation [34]

Most of the catalytic reactions involving insertion of unsaturated compounds into M–Het bond are based on M(0), M(I), or M(II) metal centers in the catalyst active site. These metal centers are expected to possess medium or strong binding energy upon coordination of multiple carbon–carbon bonds [37, 38]. The behavior can be efficiently tuned by ligands, and in case of strong binding of unsaturated compounds stable π-complex can be isolated. Insertion reaction also can be successfully mediated in weakly bound systems, for example this was demonstrated in case of Pt(IV) [18]. The possibility of direct reaction in bimolecular fashion without preliminary coordination of unsaturated molecule (Scheme 5) remains a challenging question.



Scheme 7 Insertion of alkynes and alkenes with different orientations of heteroatom groups; other isomers are also possible depending on the ligand environment (not shown)

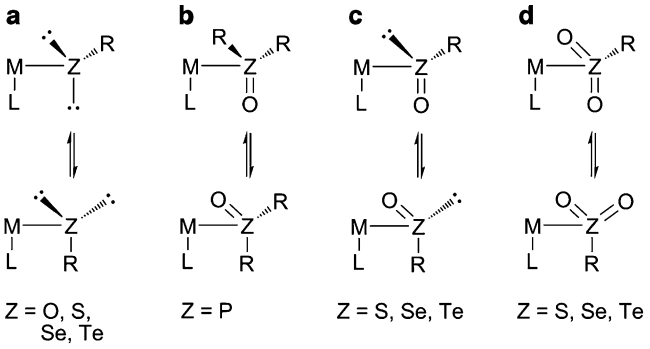
2.3 The Role of Orientation of Heteroatom Group

Typical simplified representation of the multiple bond insertion into the metal–heteroatom bond commonly used in the modern literature (Schemes 3 and 4) does not point out on possible influence of orientation of the heteroatom group. Indeed, this factor is very often neglected and here we discuss it in more detail.

Spatial arrangement of heteroatom groups covered in this volume (N, P, O, S, Se, Te) gives rise to different isomers of transition metal complexes. For nitrogen and phosphorus (III) two isomers **A** and **B** may exist due to rotation around metal–heteroatom bond (Scheme 7). In the **A-TS** the lone pair of the heteroatom interacts with the multiple carbon–carbon bond, whereas in **B-TS** direct interaction is unlikely. Such different interactions may become a reason for changing relative stability of the transition states.

The factor of orientation of heteroatom group should be considered for both types of mechanisms – "cycloaddition-like" process or attack of the heteroatom group on the coordinated multiple bond (Scheme 3).

The products **A-product** and **B-product** can be interconverted between each other due to rotation around carbon–heteroatom bond (Scheme 7). Both kinetic and thermodynamic control may be realized in the system and complicate experimental studies. Obviously, formation of either **A-product** or **B-product** cannot be considered as an evidence for involvement of **A-TS** or **B-TS**, respectively. Different factors may influence relative stability of **A** and **B**, barrier heights to overcome **A-TS** and **B-TS**, as well as relative stability of **A-product** and **B-product**. In this topic computational studies have a great potential to construct the energy surface of the reaction and to reveal the favoring pathway of the insertion reaction.



Scheme 8 Different orientations of the heteroatom groups in the initial complexes for insertion of alkenes and alkynes into the M–Z bond (coordinated multiple bond is omitted); other isomers are also possible depending on the ligand environment

A variety of different geometry orientations are accessible for other heteroatom groups as well (Scheme 8). Different isomers of the initial metal complex may initiate alternative pathways of multiple bond insertion in the same manner as described earlier (Scheme 7).

This effect can be expected for reactions involving chalcogen groups (Scheme 8a), oxidized chalcogen groups (Scheme 8c, d), as well as -P(O)R_2 and -P(O)(OR')$_2$ groups with the phosphorus center (Scheme 8b). Varying degree of interaction with the oxygen atom is an additional factor that influences potential energy surface and reactivity in the systems (Scheme 8b–d).

As a representative example of the role of orientation of heteroatom group, we can consider theoretical study of alkyne insertion involving Pd–PMe_2, Pd–P(O)Me_2, and Pd–P(O)$(OMe)_2$ bonds [39]. The insertion reaction related to hydrophosphination process was studied in the [Pd(η^2–HC≡CH)(PMe_2)(H)(PH_3)] model complex resulted from oxidative addition of the H–PMe_2 to Pd(0).

Indeed, it was found that both isomers **A** and **B** do exist on the potential energy surface and the isomer with *anti*-orientation of the phosphorus lone pair and coordinated alkyne is slightly more stable by −0.9 kcal/mol (Fig. 2 and Scheme 9). The isomers were connected by small rotational barrier of 2.8 kcal/mol, which can be easily overcome at the room temperature.

Alkyne insertion via the **A→A-TS→A-product** pathway was calculated to be exothermic by $\Delta G = -18.2$ kcal/mol and requires overcoming of the activation barrier with $\Delta G^{\neq} = 15.9$ kcal/mol (Fig. 2). The second route of the alkyne insertion through the **B→B-TS→B-product** pathway was found much more exothermic $\Delta G = -30.4$ kcal/mol and was characterized by significantly smaller activation barrier $\Delta G^{\neq} = 5.7$ kcal/mol.

The products of both pathways were connected by the rotational transition state **TS-rotation-prod** (Fig. 2). The difference in relative energy between these products originated from suitable orientation of the phosphorus group. One of the structures (**B-product**) allows stabilization of the metal center by coordination in

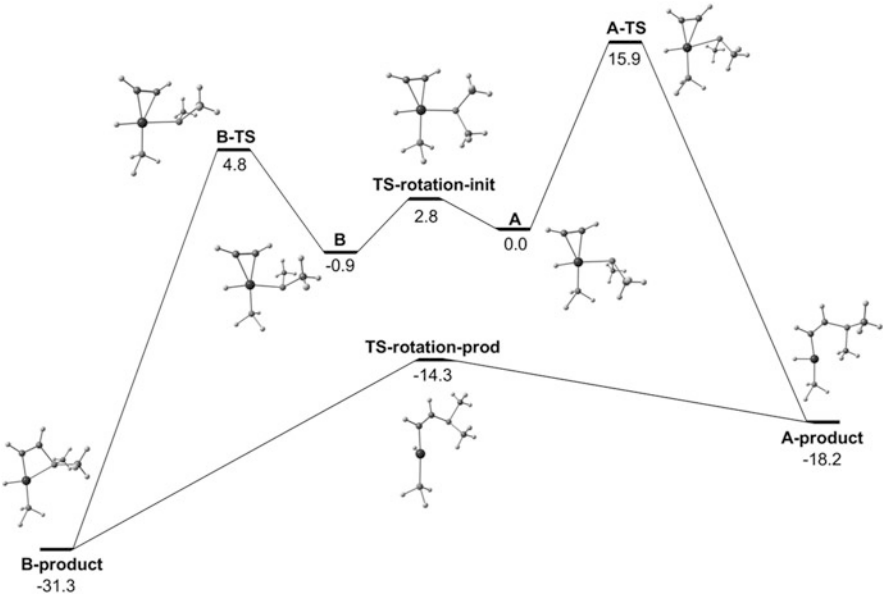
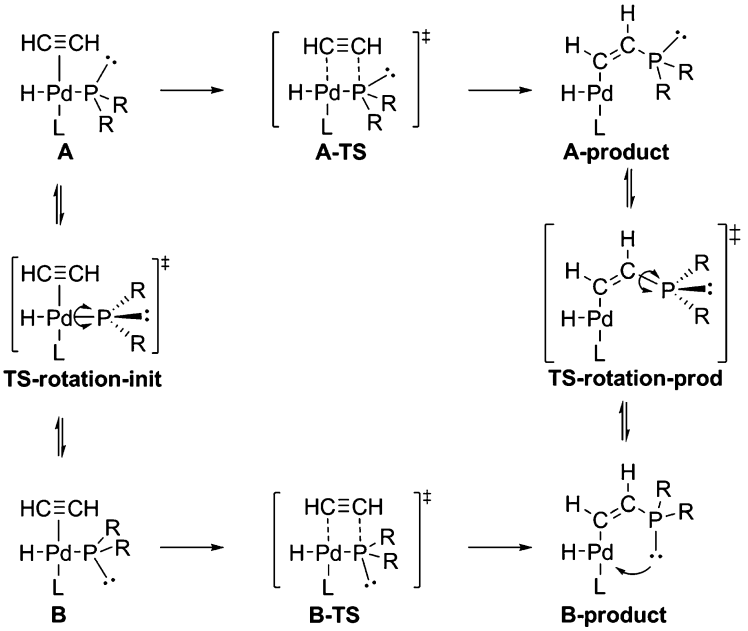


Fig. 2 Potential energy surface of the acetylene insertion into the Pd–PR_2 bond calculated at B3LYP level (L═PH_3, R═Me; see Scheme 9 for structures); ΔG values are shown in kcal/mol [39]



Scheme 9 Insertion of acetylene into the Pd–PR_2 bond [39]

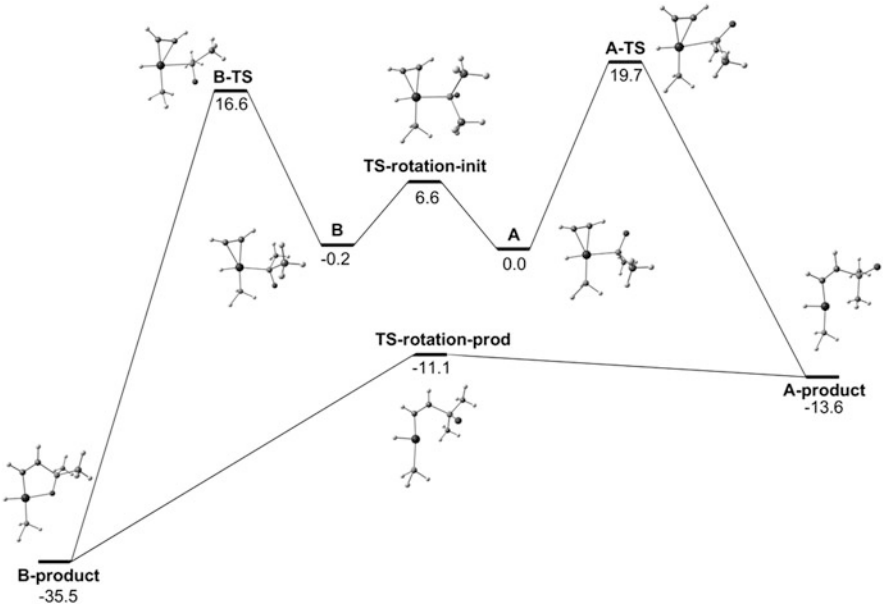


Fig. 3 Potential energy surface of the acetylene insertion into the Pd–P(O)R_2 bond calculated at B3LYP level (L═PH_3, R═Me; see Scheme 10 for structures); ΔG values are shown in kcal/mol [39]

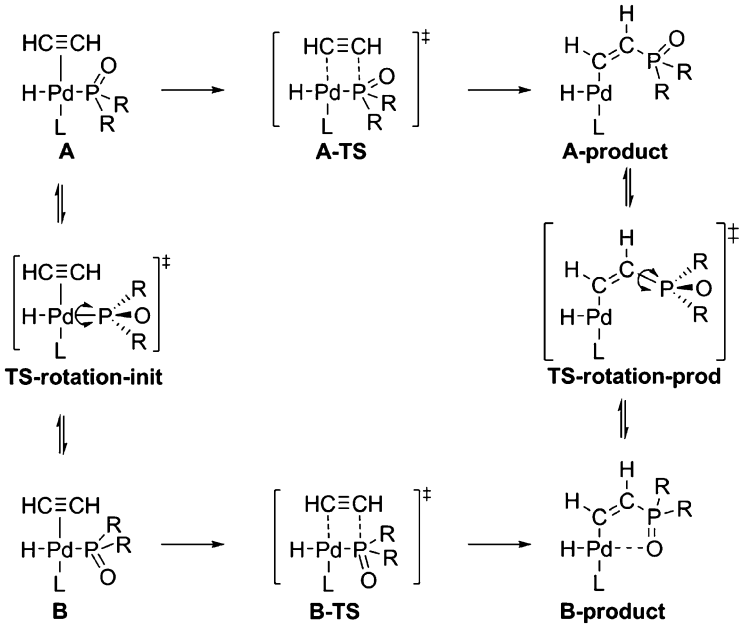
chelate fashion, whereas coordination of the phosphorus group in another case (**A-product**) was not found.

Comparison of both pathways clearly suggested that the **B→B-TS→B-product** pathway is more favorable from both kinetic and thermodynamic reasons for acetylene insertion into the Pd–PMe_2 bond.

The insertion reaction related to hydrophosphinylation process was studied in the [Pd(η^2–HC≡CH)(P(O)Me_2)(H)(L)] model complex resulted from oxidative addition of the H–P(O)Me_2 to Pd(0). Theoretical calculations of the energy surface have shown important influence of the orientation of the phosphorus group (Fig. 3 and Scheme 10) [39].

Analysis of both pathways **A→A-TS→A-product** and **B→B-TS→B-product** again suggested that the latter is clearly favorable from thermodynamic reasons for acetylene insertion into the Pd–P(O)Me_2 bond and it is also slightly favorable from kinetic reasons (Fig. 3). The relative stability of the products greatly depended on the orientation of the phosphorus group. Coordination of the oxygen atom to the metal center led to complex **B-product**, which was calculated to be more stable by 21.9 kcal/mol compared to the complex **A-product**.

The calculations highlighted the role of oxygen atom in phosphine oxide moiety: all calculated activation barriers were increased with a noticeable change of ~4 kcal/mol for the **A-TS** and **TS-rotation-init** (*cf.* Figs. 2 and 3). Nearly threefold increase of the activation barrier was calculated for the **B-TS**: $\Delta G^{\neq} = 5.7$ kcal/mol for the acetylene insertion into the Pd–PMe_2 bond (Fig. 2) and $\Delta G^{\neq} = 16.8$ kcal/mol for the acetylene insertion into the Pd–P(O)Me_2 bond (Fig. 3).



Scheme 10 Insertion of acetylene into the Pd–P(O)R_2 bond [39]

Theoretical calculations have been also carried out to study acetylene insertion into the Pd–P(O)$(OMe)_2$ bond related to hydrophosphorylation process [39]. The activation barriers for alkyne insertion were calculated to be $\Delta G^{\neq} = 21.4$ and 23.7 kcal/mol depending on the orientation of the phosphorus group. However, much smaller difference in the relative stability of the products was found. The presence of three oxygen atoms attached to the phosphorus center facilitated chelate coordination to the metal in any orientation of the phosphorus group. Thus, the influence of orientation of heteroatom group significantly depends on the number of bonded oxygen atoms (see also Scheme 8).

Interesting to note that calculated Pd–P bond energy was shown to change in the order P═P(O)$(OMe)_2$ > P(O)Me_2 > PMe_2, whereas the reactivity in the acetylene insertion reaction changed in the reversed order: Pd–P(O)$(OMe)_2$ < Pd–P(O)Me_2 < Pd–PMe_2.

2.4 *Structural Reorganization of the Initial Complex*

In order to reach proper initial structure to undergo insertion reaction, not only orientation of the heteroatom group but also geometric arrangements of the multiple bond is an important prerequisite. Structural reorganization required to achieve

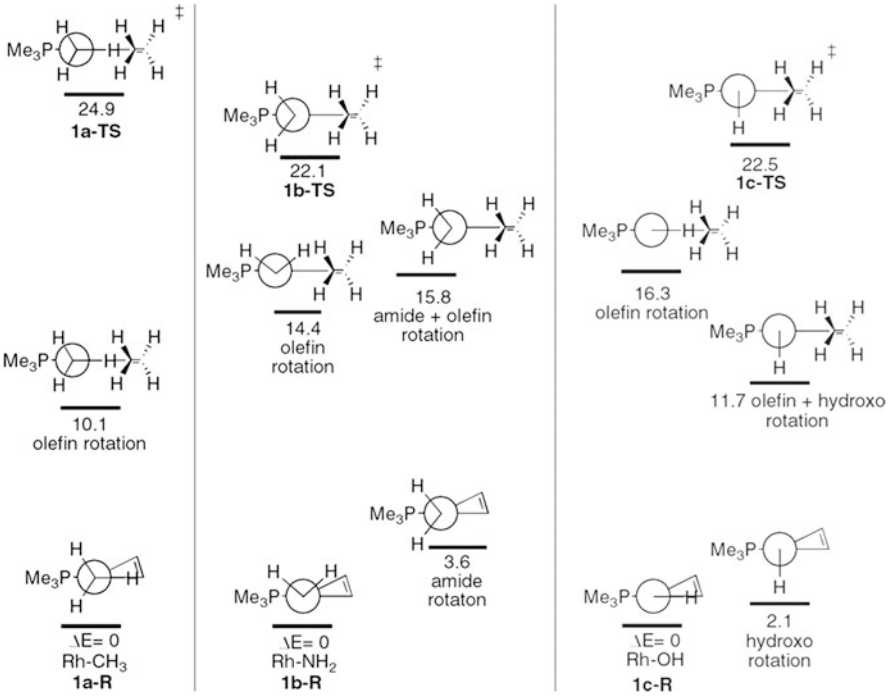


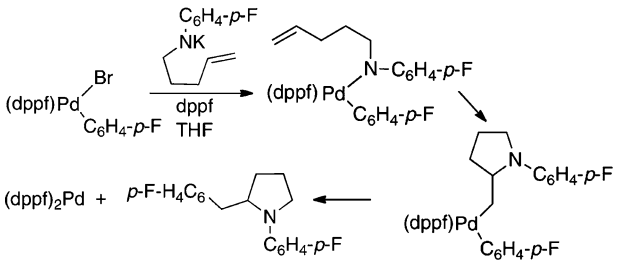
Fig. 4 Relative ΔE energies calculated at B3LYP level (in kcal/mol) for reactants (**R**), transition states (TS), and rotational isomers for ethylene insertion into the Rh–CH_3 (**a**), Rh–NH_2 (**b**), and Rh–OH (**c**) bonds [40]

initial complex and then the transition state involves geometry adjustment of coordinated multiple bond and bound heteroatom group.

Several complexes arose due to different orientations of coordinated olefin and reacting group were characterized in the theoretical study of ethylene insertion in rhodium complexes (Fig. 4) [40]. The calculations were carried out for the model system using [Rh(η^2–CH_2═CH_2)(Z)(PMe_3)] complex, where Z = CH_3, NH_2, and OH.

Constrained geometry optimization with the ethylene in the square plane (same double bond orientation as in the transition state) led to the olefin rotation structures, which were higher in energy by 10.1, 14.4, and 16.6 kcal/mol compared to the reactants for the complexes with Rh–CH_3, Rh–NH_2, and Rh–OH bonds, respectively (Fig. 4). Changes in the orientation of the –NH_2 and –OH groups (geometric arrangement of hydrogen atoms and electron pairs) resulted in appearance of several structural isomers with the energy difference in the order of 2–5 kcal/mol.

Calculated energy barriers for alkene insertion starting from the low energy reactant changed in the order: 24.9 kcal/mol for Rh–CH_3 > 22.1 kcal/mol for Rh–NH_2 and 22.5 kcal/mol for Rh–OH. However, the difference in the energy of



Scheme 11 Intramolecular insertion of alkene into the Pd–N bond [41, 43]

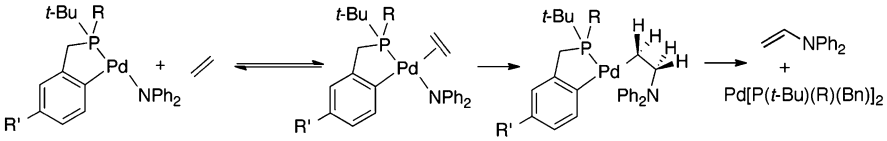
the transition state and initial structure obtained in constrained "TS-like" geometry arrangement was more specific to heteroatoms: 14.8 kcal/mol for Rh–CH_3 > 10.8 kcal/mol for Rh–NH_2 > 6.3 kcal/mol for Rh–OH (Fig. 4) [40].

Thus, the study has demonstrated that structural reorganization of reacting fragments in the coordination sphere of the metal makes a large contribution in the order of 10–16 kcal/mol to the overall activation barriers of 22–25 kcal/mol.

2.5 *Selectivity of the Insertion Reaction, Steric and Electronic Effects*

Experimental evidence for insertion of alkenes into the metal–nitrogen bond was reported recently in the studies of aminopalladation reactions [41, 42]. Intramolecular insertion reaction was confirmed to be a *syn*-addition process and was monitored by NMR spectroscopy of the well-defined palladium(aryl)(amido) complexes (Scheme 11) [41, 43]. The reaction proceeded as insertion into Pd–N bond with complete chemoselectivity and the alternative route of alkene insertion into the Pd–C bond was not observed. The activation enthalpy determined for the insertion step $\Delta H^{\neq} = 24.8 \pm 0.6$ kcal/mol was comparable with the values reported for other insertion reactions, and small activation entropy $\Delta S^{\neq} = 4.6 \pm 1.8$ eu is consistent with intramolecular transformation [41, 43]. The final product of the reaction was formed after C–C reductive elimination, which is known to be rather fast step if at least one aryl group is involved [44, 45]. The mechanistic study of the alkene insertion into the Pd–N bond has also pointed out on possible reversible nature of such process [46].

Intermolecular alkene insertion into the Pd–N bond was shown to be a *syn*-addition process as well (Scheme 12) [42, 47]. Amido complexes of palladium were found to coordinate alkene, undergo migratory insertion and finally to form enamine product after β-hydrogen elimination. Experimental evidence for the ethylene amido intermediate and for *syn*-addition process was obtained by NMR spectroscopy, including deuterium labeling study. The rate constant of the decay of observed intermediate complexes leading to the formation of the enamine corresponded to $\Delta G^{\neq}$ of 17 kcal/mol (8.7×10^{-4} s^{-1}, −40°C) [42].



Scheme 12 Intermolecular insertion of alkene into the Pd–N bond [42, 47]

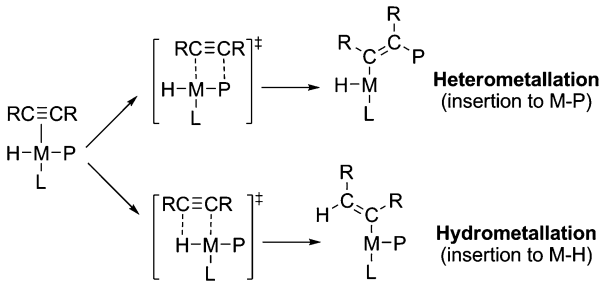
Important factors that govern reaction rates of the insertion process are heteroatom basicity/nucleophilicity and steric/electronic effects in the ligands and substrates [43, 47]. Particularly, it was reported that bulky ligands and electron-poor alkenes lower the barrier of migratory insertion. The origin of the steric effect came from a stronger influence of the ligand in the initial state of the complex, rather than in the transition state (in the transition state alkene lies along the Pd–N bond, see Fig. 3). The origin of the electronic effect was proposed due to electron density delocalization between the metal center and double bond upon coordination and movement toward the transition state.

In the case of alkynes obtaining the data on the stereoselectivity of the insertion process is straightforward since *Z*/*E*-geometry of the double C═C can be easily determined in intermediate complexes and in the products (cf. Schemes 3 and 4). For example, the intermediate complexes dealing with metal–chalcogen bonds transformations were isolated and structurally characterized [48, 49], as well as the insertion pathway was characterized by theoretical calculations for homogeneous catalysis with molecular complexes [50] and for heterogeneous catalysis with nanoparticles [51]. The topic is discussed in detail for various heteroatoms and metal complexes in the other chapters of this book [20–28].

It is accepted that insertion reaction proceeds with complete intrinsic selectivity – only *syn*-addition species are expected. However, the overall selectivity of the catalytic reaction and the yield of the product nevertheless can vary in a wide range. Considering the mechanism, the overall outcome of the catalytic procedure depends on the regioselectivity of the insertion and on the M–Het vs. M–H insertion pathways (Scheme 2). The latter issue is of principal importance to design new catalytic systems and deserves a special note.

Catalytic hydrofunctionalization of the multiple bonds involves oxidative addition of H–Het to low valent metal complex and intermediate formation of H–ML_n–Het complex. As a next step, either heterometallation (insertion into M–Het) or hydrometallation (insertion into M–H) may take place (Scheme 13). Involvement of both pathways was proposed in practical hydrofunctionalization reactions with various substrates and different metal complexes [20–28].

Comparative theoretical study at density functional, MP2, and ONIOM levels was carried out for H–M–P complexes to reveal the difference in reactivity of M–P and M–H bonds toward the alkyne (Scheme 13) [39, 52, 53]. Theoretical analysis was carried out for different metals, ligands [52, 53], and conformations [39]. The computational study has clearly shown that alkyne insertion into the M–H bond is much more kinetically preferred with calculated activation barriers of $\Delta E^{\neq}$ = 1.0–6.1 kcal/mol, compared to higher barriers of $\Delta E^{\neq}$ = 15.1–28.2 kcal/mol



Scheme 13 Alkyne insertion through the hydrometallation vs. heterometallation pathways [39, 52, 53]

for alkyne insertion into the M–P bond [52]. The scope of the reaction was verified for different metals (M = Ni, Pd, Pt, and Rh) and ligands (L = PH_3 and PPh_3). The relative reactivity of the metal complexes in the reaction with alkynes was estimated in the calculations and was shown to decrease in the following order: Ni > Pd > Rh > Pt. A relative trend in the reactivity was established for various types of phosphorus groups: PR_2 (most reactive) > P(O)R_2 (intermediate) > P(O)$(OR)_2$ (less reactive), which showed a decrease upon increasing the number of the oxygen atoms attached to the phosphorus center.

Such a large difference in the reactions of M–Het and M–H bonds with unsaturated groups provides a valuable insight for design of novel catalytic systems. If both reacting groups (hydrogen and heteroatom) are available for the insertion, the reaction involving M–H bond should proceed first. Insertion into the M–Het bond becomes possible only if M–H bond is not present in the complex or it is not available for reaction. This provides a clear hint to control direction of the reaction and to influence the selectivity by stabilization/destabilization of metal hydrides and by ligand control over the available insertion channels in the coordination sphere of the metal. An illustration on the ligand control over the M–H/M–Het insertion has been reported recently for the hydrothiolation reaction catalyzed by Rh–NHC complexes [54].

It is of much interest to reveal to what extent such significant difference in reactivity of M–H/M–Het bonds will remain for other transition metal complexes and heteroatoms.

3 Conclusions

In spite of very common mentioning of insertion process in a variety of modern studies and in spite of widespread application of addition reactions in modern organic chemistry, molecular picture of this fascinating transformation remains unexplored. The aim of this chapter is to point on understanding at molecular level of insertion (migratory insertion) of unsaturated organic molecules into metal–heteroatom bond.

Detailed consideration of geometry/orientation of coordinated multiple bond and heteroatom group provides a new look on the role of ligand environment and opens new possibilities for catalyst design. Important factors for the reactivity issue are: (1) stabilization of favorable structure of the initial complex (Fig. 4); (2) adjustment of π-complex strength (Fig. 1); and (3) control over the spatial movement of heteroatom group (Figs. 2 and 3). Improvement of selectivity of catalytic synthetic procedures recalls for better understanding of: (1) heterometallation vs. hydrometallation pathways (Scheme 13); (2) regioselectivity of the alkyne insertion step (Scheme 2); and (3) steric and electronic effects of substituents in heteroatom group and in substrate.

We anticipate further mechanistic studies and applications in organic synthesis of these powerful metal-mediated transformations.

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The Mechanism for Transition-Metal-Catalyzed Hydrochalcogenation of Unsaturated Organic Molecules

Akihiko Ishii and Norio Nakata

Abstract In this chapter, discussions are focused on two types of mechanisms of transition-metal-catalyzed hydrochalcogenation, Type I and Type II, which are classified by the initial behavior of precatalysts. In Type I mechanism, precatalyst M–X (M = Pd, Ni, Zr, Ln, and An) first undergoes protonolysis with REH (E = O, S, and Se) to generate active catalyst M–ER, which then undergoes insertion of alkyne into the M–ER bond (chalcogenometalation) to give 2-chalcogenovinyl complex, followed by protonolysis of M–C_{vinyl} with REH to produce the product and to regenerate active catalyst M–ER. Type II mechanism starts from oxidative addition of REH (E = S and Se) to complex [M] (M = Pd, Pt, Rh, and Ir) to give chalcogenolato–hydrido complex, [M]H(ER). In the next alkyne insertion, [M]–H insertion (hydrometalation) to give [M](ER)(vinyl) or [M]–E insertion (chalcogenometalation) to give [M]H(2-RE-vinyl) occurs and then reductive elimination of the resulting vinyl [M] complexes yields the product and [M]. Reactions where transition metal catalysts exert as Lewis acid to activate unsaturated bonds and those proceeding through vinylidene intermediates are mentioned only shortly.

Keywords Hydrochalcogenation · Oxidative addition · Protonolysis · Reductive elimination · Transition metal

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1 Introduction

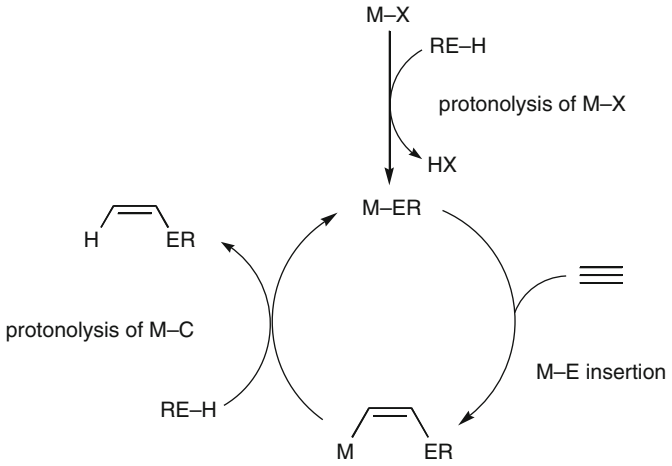
Introduction of organoelemento functionalities into organic molecules is an important reaction to prepare useful synthetic intermediates [1–8]. This chapter concerns the mechanism of transition-metal-catalyzed addition of chalcogenol (REH: E = O, S, and Se) to carbon–carbon unsaturated bonds. Conventional additions of REH, catalyzed by Brønsted acids or initiated by radical species, and chalcogenolate (RE^-) to unsaturated bonds are out of scope of this chapter. In the transition-metal-catalyzed hydrochalcogenation, discussions are focused on two types of mechanisms, Type I and Type II, which are classified by the initial behavior of precatalysts for convenience and involve at least one step of insertion of carbon–carbon unsaturated bond to metal–chalcogen (M–E) or metal–hydrogen (M–H) bonds. In some cases, this classification is ambiguous and there are hybrid type mechanisms of them. Reactions where transition metal catalysts exert as Lewis acid to activate unsaturated carbon–carbon bonds and those proceeding through vinylidene intermediates are mentioned only shortly in this introduction part.

1.1 Type I Mechanism

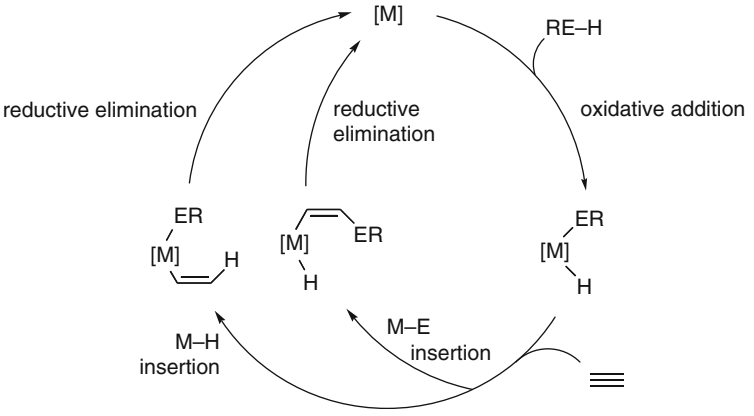
In the initial stage of this mechanism (Scheme 1), transition metal precatalyst M–X undergoes protonolysis of the M–X bond with REH to generate active catalyst M–ER. The chalcogenolato–metal complex then undergoes insertion of alkyne into the M–ER bond (chalcogenometalation) to give 2-chalcogenovinyl complex. In the final stage, protonolysis of $M–C_{vinyl}$ with REH produces the product and active catalyst M–ER.

1.2 Type II Mechanism

Type II mechanism starts from oxidative addition of REH to transition metal complex ([M]) to give chalcogenolato–hydrido metal complex, [M]H(ER) (Scheme 2). In the next step of alkyne insertion, there are two possible pathways, [M]–H insertion (hydrometalation) to give [M](ER)(vinyl) and [M]–E insertion (chalcogenometalation) to give [M]H(2-RE-vinyl). In the final stage, reductive



Scheme 1 Catalytic cycle for Type I mechanism comprising of protonolysis of M–X by REH, M–E insertion of alkyne, and protonolysis of M–C_{vinyl} by REH



Scheme 2 Catalytic cycle for Type II mechanism comprising of oxidative addition of REH to transition metal complex [M], insertion of alkyne into [M]–H or [M]–E, and reductive elimination of [M](ER)(vinyl) or [M]H(2-RE-vinyl)

elimination of the resulting vinyl [M] complexes yields the product and [M]. The [M]–H insertion corresponds to Chalk–Harrod Mechanism in hydrosilylation, and the [M]–E insertion to modified Chalk–Harrod Mechanism in hydrosilylation. In the hydrosilylation, theoretical study on the reaction of $PtH(SiR_3)PH_3$ with ethylene showed that ethylene is inserted into the Pt–H bond with a lower activation energy than into the Pt–SiR_3 bond [9].

1.3 Transition Metal Catalysts as Lewis Acids

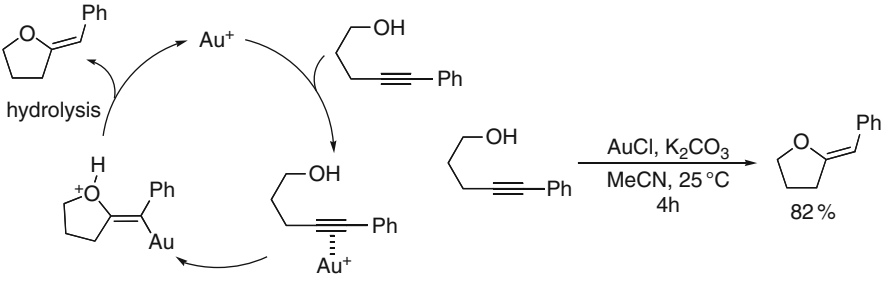
Alkynes, allenes, and alkenes in the presence of Au, Ag, or Pt complexes undergo intermolecular or intramolecular addition of X–H bond (X = O, S, and N) to yield respective hydroelementation products [10, 11]. Although mechanistic aspects are not always clarified, activation of multiple bonds with these noble metal complexes, as Lewis acids, by coordination, is proposed in some papers [12–18]. An example is shown in Scheme 3 [16].

1.4 Mechanism Through Vinylidene Intermediates

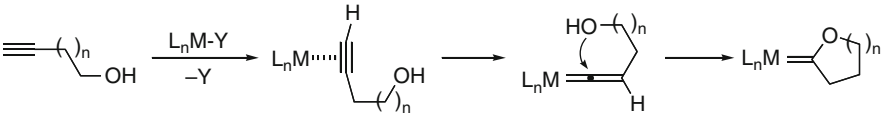
This pathway involves cycloisomerization of η^2-metal–alkyne complex to a vinylidene complex (Scheme 4) [19]. An example is shown in Scheme 5 [20]. The initial η^2-Mo–alkyne complex rearranges to vinylidene–Mo complex intermediate that undergoes an intramolecular nucleophilic attack of the hydroxy oxygen to give cyclic anionic intermediate, protonation of which yields 2,3-dihydrofuran.

2 Type I Mechanism

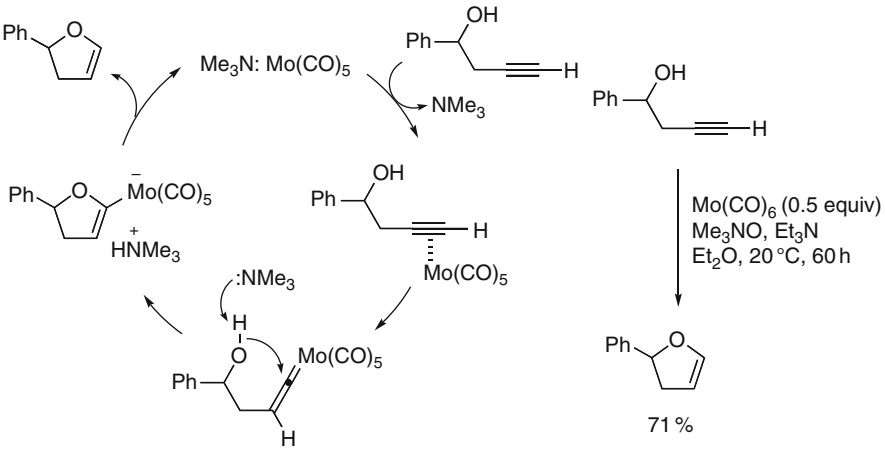
In 1992, the first examples of $Pd(OAc)_2$-catalyzed hydroselenation [21] and hydrothiolation [22] were reported by Ogawa and Sonoda and their coworkers of Osaka University. Extensive studies by the Osaka group on reaction mechanism



Scheme 3 Proposed catalytic cycle for AuCl-catalyzed intramolecular cyclization of 5-hydroxy-1-phenyl-1-pentyne



Scheme 4 Cycloisomerization of η^2-metal–alkyne complex to a vinylidene complex



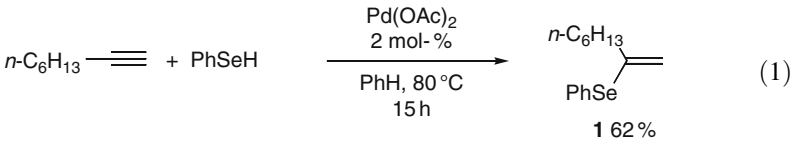
Scheme 5 Proposed catalytic cycle for Mo-catalyzed intramolecular cyclization of 4-hydroxy-4-phenyl-1-butyne

have established Type I mechanism. Subsequently, Ni(II) and groups III and IV transition-metals-catalyzed hydrochalcogenations categorized to Type I mechanism were reported.

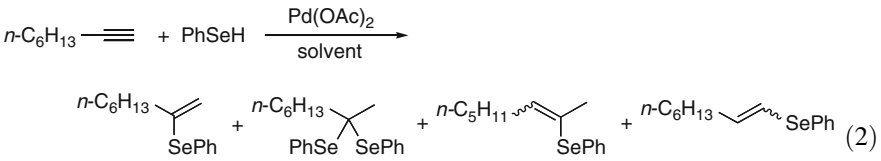
2.1 Group X Metal-Catalyzed Hydrothiolation and Hydroselenation

2.1.1 $Pd(OAc)_2$-Catalyzed Hydrothiolation and Hydroselenation

The reaction of 1-octyne with PhSeH in the presence of $Pd(OAc)_2$ in benzene at 80°C for 15 h provided the Markovnikov-type adduct, 2-(phenylseleno)-1-octene (**1**) in 62% yield (1) [21]. The reaction conducted in toluene with employing 40 mol% of pyridine or 2,2′-bipyridyl as an additive produced **1** in 38 or 63% yields, respectively. In addition, the solvent effect is remarkable and pyridine is the best solvent to form **1** (2).



(1)

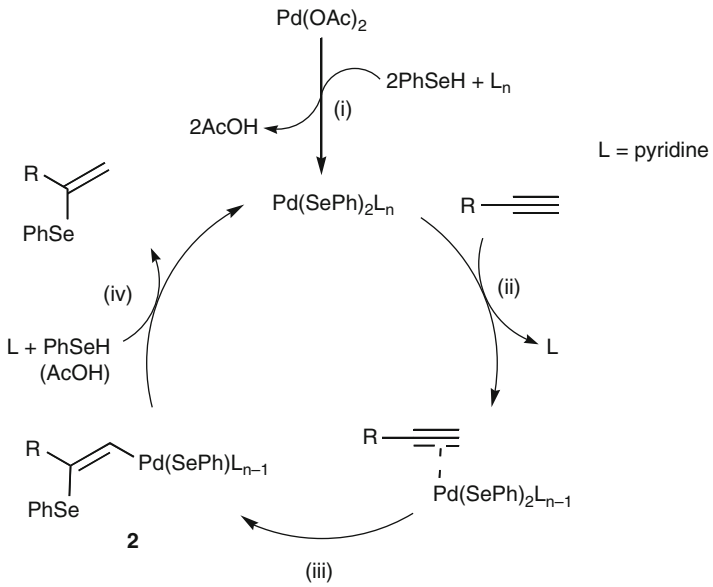


1

solv.				
THF	46	15	10	5
toluene	23	29	34	0
pyridine	77	0	0	0

These results strongly suggest that pyridine acts as a suitable ligand for an active palladium intermediate. In the absence of pyridine, palladium selenide [$Pd(SePh)_2$] molecules, a key species for this hydroselenation of alkynes, easily react with each other by the coordination of the selenide ligand to the other palladium center to form polymerized complex, which is insoluble in usual organic solvent and loses the catalytic activity. Therefore, pyridine is considered to inhibit the polymerization and protect the catalyst from the poisoning [23].

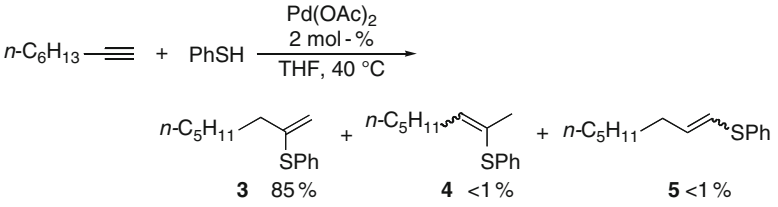
A mechanism shown in Scheme 6 was proposed [23], which involves (i) ligand exchange of the AcO group with the PhSe group to give $Pd(SePh)_2L_n$ as an active catalyst and AcOH; (ii) coordination of alkyne to the selenolato Pd(II) species; (iii) insertion of alkyne into the Pd–Se bond (*syn*-selenopalladation) to form (*Z*)-(2-phenylseleno)vinyl Pd(II) intermediate **2**; (iv) the protonolysis of the



Scheme 6 Catalytic cycle for $Pd(OAc)_2$-catalyzed hydroselenation of alkynes

vinyl Pd(II) complex **2** with PhSeH (or AcOH) to provide 2-phenylseleno-1-alkene with regeneration of the catalyst.

In the case of $Pd(OAc)_2$-catalyzed hydrothiolation of alkynes, THF was used as the solvent. Thus the reaction of 1-octyne with PhSH in the presence of $Pd(OAc)_2$ at 40°C gave **3**, **4**, and **5** in 85%, <1%, and <1% yields, respectively (3) [22].

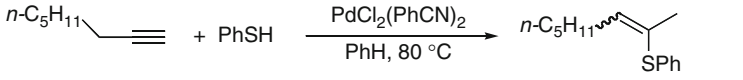


(3)

The reaction of $Pd(OAc)_2$ with 3 equiv of PhSH in THF-d_8 immediately gave dark brown precipitates and ca. 2 equiv of AcOH. This precipitate scarcely exhibited the catalytic activities for the addition of PhSH to 1-octyne. On the other hand, the precipitates prepared in the presence of 1-octyne had a moderate catalytic activity. *cis*-Addition of PhSH to 1-octyne was confirmed by the reaction employing 1-octyne-*1*-*d*. The (*E*)-isomer, (*E*)-*n*-C_6H_{13}(PhS)C=C(D)H, is the kinetic product and gradually isomerized to the (*Z*)-isomer. A mechanism similar to that shown in Scheme 6 was proposed [22].

2.1.2 $PdCl_2L_2$-Catalyzed Hydrothiolation and Hydroselenation

The reaction of terminal alkynes with a catalytic amount of $PdCl_2(PhCN)_2$ [24] or $PdCl_2(PPh_3)_2$ [25] in benzene at 80°C gave selectively **4** or **6**, respectively [(4) and (5)]. The stoichiometric reaction of $PdCl_2(PhCN)_2$ with PhSH (2 equiv) in benzene at room temperature gave a reddish brown solid with the composition of $[PdCl(SPh)(PhSH)]_n$ ($n = 1$ or 2), which catalyzes the addition of PhSH to 1-octyne in benzene at 80°C to lead to **4**. The complex also catalyzed the isomerization of Markovnikov-type adduct **3** to **4**. Scheme 7 shows a proposed catalytic cycle for $PdCl_2(PhCN)_2$-catalyzed hydrothiolation involving the isomerization of the initial Markovnikov-type adduct [24]. A similar mechanism was proposed for $PdCl_2(PPh_3)_2$-catalyzed hydroselenation [25].



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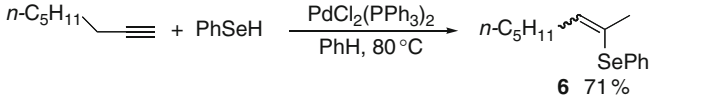

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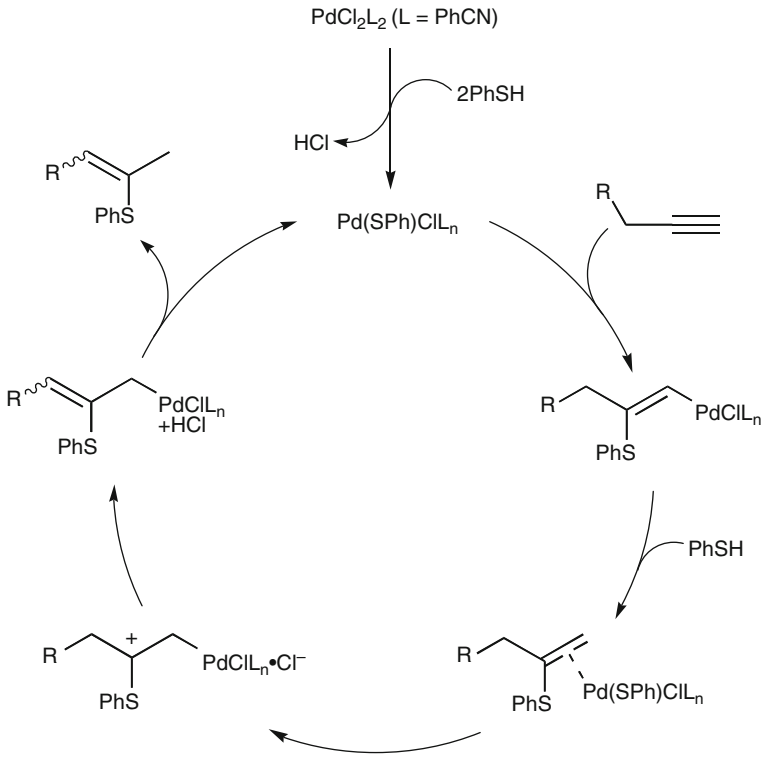
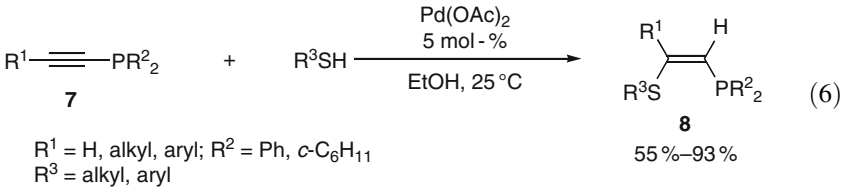


Scheme 7 Catalytic cycle for $PdCl_2(PhCN)_2$-catalyzed hydrothiolation of alkynes followed by isomerization of the resulting Markovnikov-type adduct

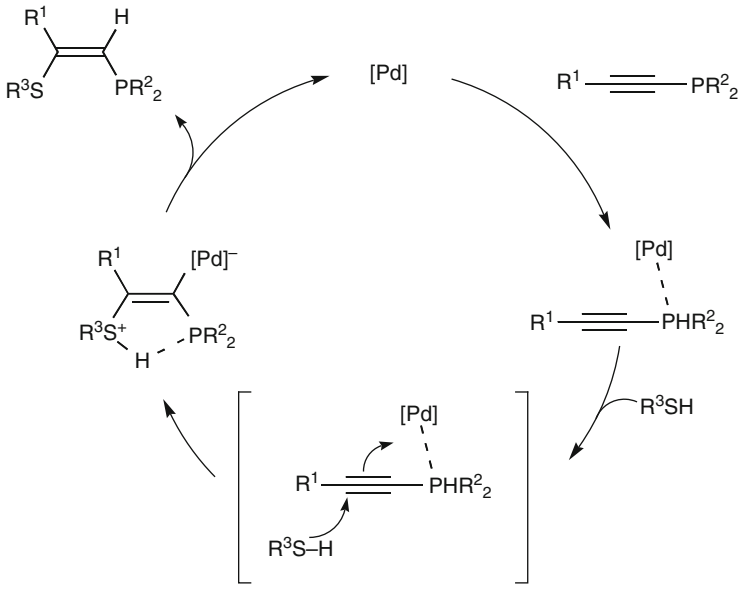
The $Pd(OAc)_2$-catalyzed hydrothiolation of 1-alkynylphosphines **7** was reported in 2007 [26]. This reaction yields (*Z*)-1-phosphino-2-thio-1-alkenes **8** regio- and stereoselectively in *anti*-hydrothiolation fashion (6). From the stereochemistry observed, the following mechanism was proposed, where Pd(II) coordinates on the phosphorus atom to induce the addition of RSH (Scheme 8).



(6)

2.1.3 Ni(II)-Catalyzed Hydrothiolation and Hydroselenation

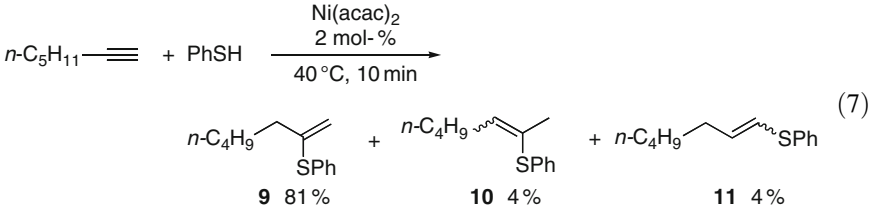
The hydrothiolation and hydroselenation of alkynes catalyzed by $NiCl_2$ [27] or $Ni(acac)_2$ [28–30] under heterogeneous conditions and by CpNi(NHC)Cl



Scheme 8 Catalytic cycle for $Pd(OAc)_2$-catalyzed hydrothiolation of 1-alkynylphosphines

(Cp = C_5H_5, NHC = *N*-heterocyclic carbene) under homogeneous conditions [31] have been reported.

The hydrothiolation of 1-heptyne with PhSH (2 equiv) was catalyzed by Ni (acac) (2 mol%) at 40°C under solvent-free conditions to produce **9**, **10**, and **11** in 81%, 4%, and 4% yields, respectively (7). In the reaction, the formation of an insoluble dark brown polymer $[Ni(SAr)_2]_n$ was confirmed by elemental analysis [28], and it was verified that the polymer served as the catalyst for the reaction of HC≡CC(OH)Me_2 with PhSH to give the corresponding Markovnikov-type product in 95% yield. The structure and morphology of the particles of $[Ni(SAr)_2]_n$ were studied by scanning electron microscopy (SEM) [28, 30, 32]. A catalytic cycle for the Ni(acac)-catalyzed hydrothiolation was proposed as shown in Scheme 9 [28, 29]. The resulting *syn*-addition of thiols to alkynes was verified by the reactions employing internal alkynes [28, 29]. A similar mechanism was proposed for the Ni $(acac)_2$-catalyzed hydroselenation [30].



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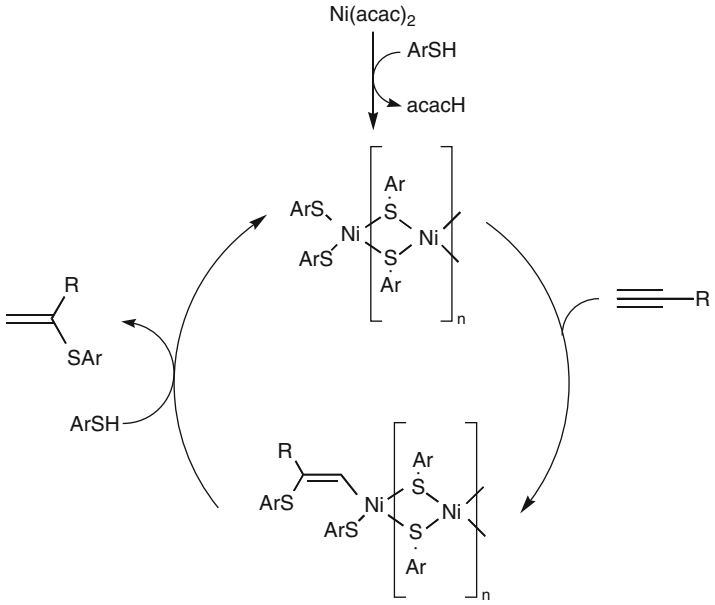
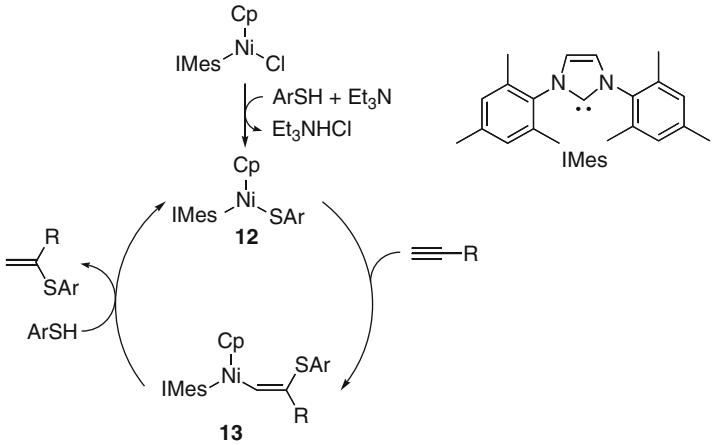


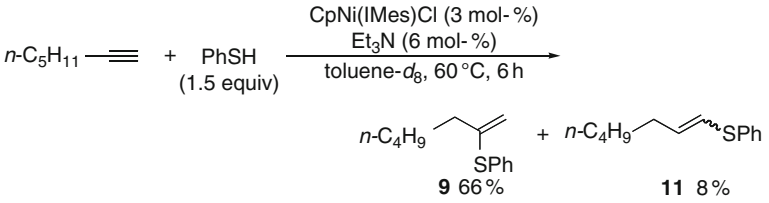
Scheme 9 Catalytic cycle for $Ni(acac)_2$-catalyzed hydrothiolation of alkynes



Scheme 10 Catalytic cycle for CpNi(IMes)Cl-catalyzed hydrothiolation of alkynes

Homogeneous hydrothiolation of alkynes was achieved by using CpNi(IMes)Cl (IMes = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene). Under the optimized conditions (8), CpNi(IMes)Cl catalyzed the reaction of PhSH with 1-heptyne in the presence of Et_3N in toluene-d_8 to give **9** (66%) and **11** (8%) without other byproducts. This catalytic reaction (Scheme 10) starts from the formation of the thiolato Ni(II)

complex **12**. Indeed, **12** (Ar = Ph) was prepared by the stoichiometric reaction of CpNi(IMes)Cl with PhSH in the presence of Et_3N (the structure was determined by X-ray crystallography) and was verified to catalyze the hydrothiolation of 1-heptyne with PhSH. Although the next intermediate **13**, formed by the insertion of alkyne to the Ni–S bond, was not observed by NMR in the reaction of **12** (Ar = *p*-$MeOC_6H_4$) with 1-heptyne, the authors proposed that **13**, being very unstable and in equilibrium with **12** and alkyne, was trapped by ArSH to give the product by protonolysis of the Ni–C_{vinyl} bond [31].

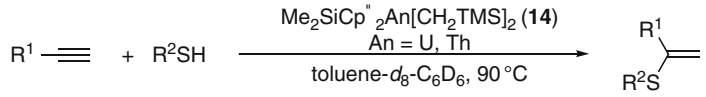


(8)

2.2 *Groups III and IV Metal-Catalyzed Hydrothiolation and Hydroalkoxylation*

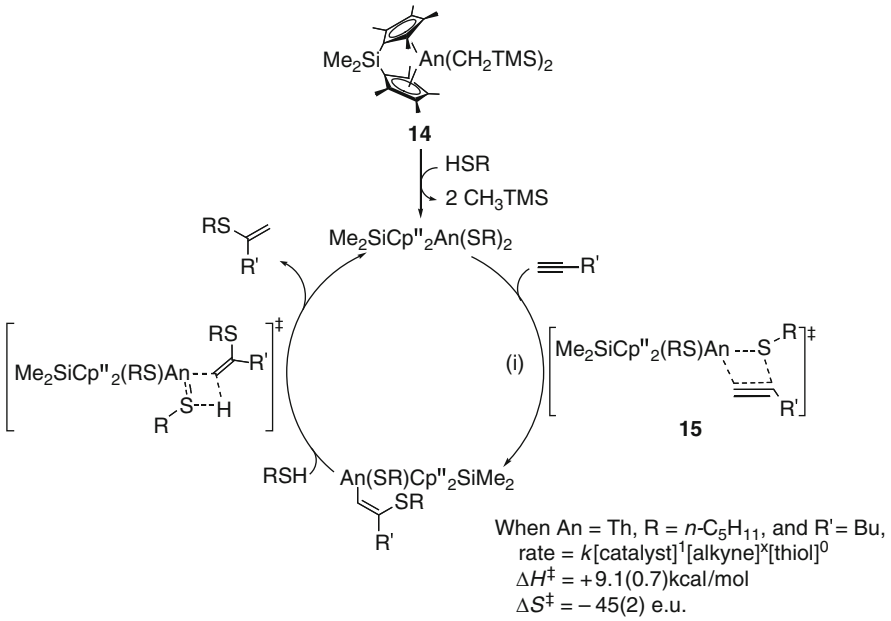
2.2.1 Organoactinide- and Organolanthanide-Catalyzed Hydrothiolation

Organoactinide complexes catalyze the hydrothiolation of alkanethiols and arenethiols into alkyl, aryl, and vinyl alkynes. The reaction catalyzed by $Me_2SiCp''_2An(CH_2TMS)_2$ (**14**) (An = U, Th; Cp″ = C_5Me_4) yields Markovnikov-type adducts regioselectively (9) [33].



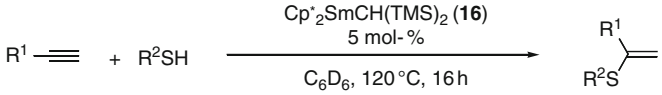
(9)

Monitoring the reaction reveled that $Me_2SiCp''_2Th(CH_2TMS)_2$ (**14**: An = Th) underwent fast Th–CH_2TMS bond protonolysis in the presence of excess thiol. The rate-limiting step in the catalytic cycle is the alkyne insertion step into Th–SR bond [Scheme 11, (i)], because kinetic study on the reaction of 1-pentanethiol with 1-hexyne in the presence of **14** (An = Th) showed that the reaction obeyed first-order in [**14** (An = Th)], first-order in [alkyne] at lower alkyne concentration and zero-order at higher [alkyne], and zero-order in [thiol]. Kinetic analysis between 60 and 110°C gave $\Delta H^{\ddagger}$ = +9.1(0.7) kcal mol^{-1} and $\Delta S^{\ddagger}$ = −45(2) e.u., suggesting a highly ordered (four-membered) transition state **15**. The kinetic isotope effect is k_H/k_D = 1.35(0.1) in the reaction. In the reaction of *n*-$C_5H_{11}SD$ with 1-hexyne in the presence of **14** (An = Th), deuterium was introduced at both *E* and *Z* positions because deuterium exchange between *n*-$C_5H_{11}SD$ with 1-hexyne occurred by reversible alkyne C–H activation.



Scheme 11 Catalytic cycle for organoactinide-catalyzed hydrothiolation

Marks and coworkers also reported in detail the Markovnikov-selective lanthanide-mediated, intermolecular hydrothiolation of terminal alkynes by aliphatic, benzylic, and aromatic thiols using $Cp^*_2LnCH(TMS)_2$ ($Cp^* = C_5Me_5$; Ln = La, Sm (**16**), and Lu) as precatalysts [34]. The Markovnikov selectivity and conversion rate of this transformation depend on the bulkiness of substituents of thiols and alkynes (10).



(10)

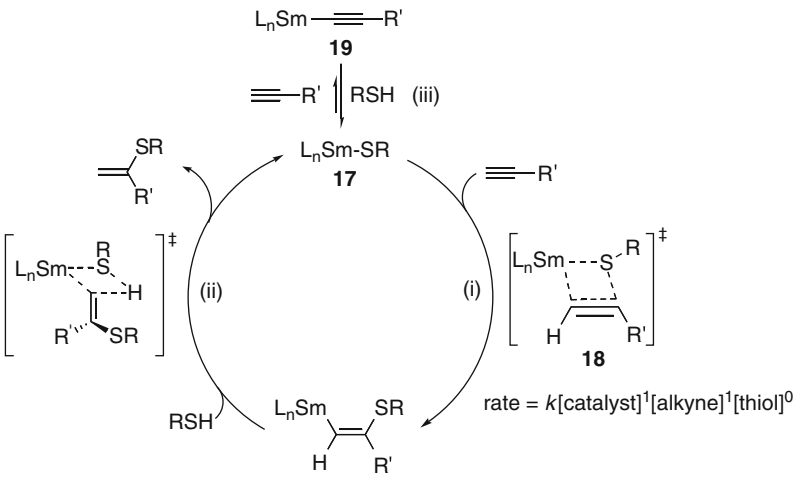
R^1 = *n*-C_4H_9, *c*-C_6H_{11}, *c*-$C_6H_{11}CH_2$, $PhCH_2$, Ph, 3-pyridyl, 1-cyclohexenyl

R^2 = Et, *n*-C_5H_{11}, *c*-C_6H_{11}, $PhCH_2$, Ph

conversion: 11 % – >95 %

Markovnikov selectivity: 32 % – >99 %

The proposed mechanism is shown in Scheme 12. The $Cp^*_2SmCH(TMS)_2$ (**16**)-mediated reaction between 1-pentanethiol and 1-hexyne was found to be first-order in catalyst concentration, first-order in alkyne concentration, and zero-order in thiol concentration by kinetic investigations. The reaction of **16** with >20 equiv of 1-pentanethiol and 1-hexyne in benzene-d_6 was monitored by NMR to show the formation of $H_2C(TMS)_2$ and 40–60% of Cp*H, indicating occurrence of the protonolysis of not only $CH(TMS)_2$ but also Cp* in **16** by thiol in the catalyst activation stage to generate **17**. The reactions employing thiols and terminal alkynes bearing a sterically demanding substituent showed the decrease of the

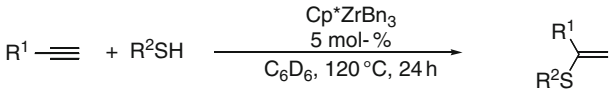


Scheme 12 Catalytic cycle for organolanthanide-catalyzed hydrothiolation

selectivity of Markovnikov addition to *anti*-Markovnikov addition, suggesting a strong dependence of hydrothiolation activity on the steric hindrance in the four-membered transition state **18**. The formation of *anti*-Markovnikov adducts is suppressed in the presence of γ-terpinene as a radical inhibitor, indicating that a free radical mechanism is operative for the *anti*-Markovnikov addition. The reaction with deuterium-labeled alkyne (Ph–C≡C–D) reveals a secondary kinetic isotope effect [$k_H/k_D = 1.40(0.1)$] and deuterium exchange between alkyne –C≡C–D and thiol RS–H. The kinetic isotope effect indicates that insertion of alkyne to Sm–SR bond (i) is the turnover-limiting process followed by fast thiol-induced Sm–C bond protonolysis (ii). Observed deuterium exchange between alkyne –C≡C–D and thiol RS–H shows the equilibrium between **17** and **19** (iii), favoring the Sm–SR species **17** under hydrothiolation conditions.

2.2.2 Organozirconium(IV)-Catalyzed Hydrothiolation

Organozirconium(IV)-catalyzed hydrothiolation of terminal alkynes was studied with $[Me_2Si(Cp'')N\text{-}t\text{-}Bu]ZrMe_2$ ($Cp'' = C_5Me_4$) (**20**), Cp^*ZrBn_3, $Cp^*ZrCl_2NMe_2$, $Cp^*_2ZrMe_2$, and $Zr(NMe_2)_4$ as the precatalysts [35]. The choice of ligands on zirconium is important for decongestion of the metal center for further reactions and for preventing the aggregation of the resulting thiolato-zirconium complexes leading to unfavorable precipitation. Thus, $Cp^*ZrCl_2NMe_2$, **20**, and Cp^*ZrBn_3, which have one cyclopentadienyl-based ligand, showed high reactivity and $Cp^*_2ZrMe_2$ showed low reactivity. $Zr(NMe_2)_4$ exhibited high initial activity but resulted in gradual precipitation. Equation (11) summarizes the hydrothiolation with Cp^*ZrBn_3 as the precatalyst. The hydrothiolation is highly Markovnikov-selective (up to 99%), and the formation of *anti*-Markovnikov products is suppressed by the addition of a radical inhibitor.

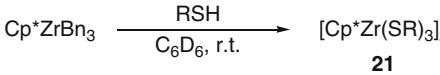


(11)

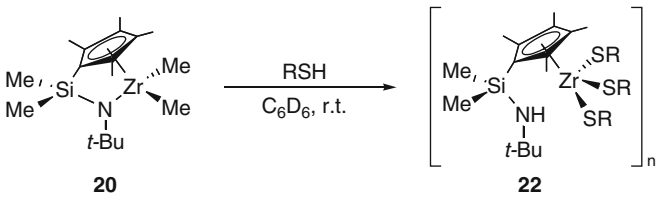
R^1 = *n*-C_4H_9, *c*-C_6H_{11}, *c*-$C_6H_{11}CH_2$, $PhCH_2$, Ph, 3-pyridyl, 1-cyclohexenyl — conversion: 79 % – quant; Markovnikov selectivity: 66 % – 99 %

R^2 = Et, CF_3CH_2, *n*-C_5H_{11}, $PhCH_2$, Ph

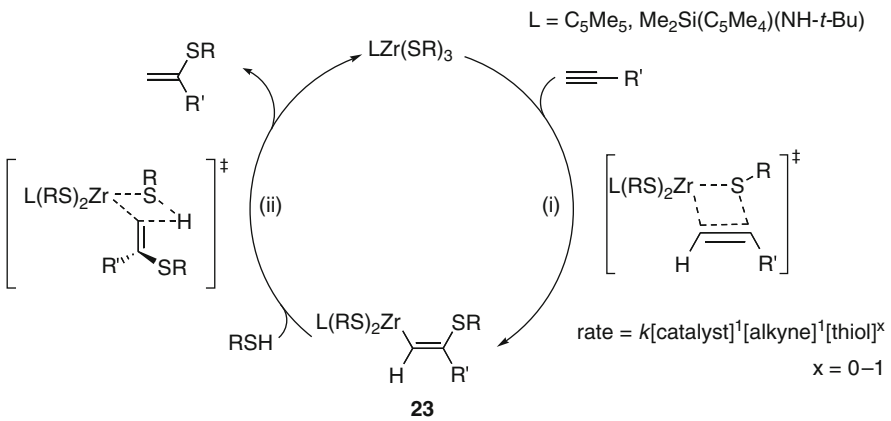
The formations of dimer **21** or oligomer **22** of tris(thiolato) Zr(IV) complexes were observed by ^{1}H NMR [(12) and (13)]. Kinetic studies on **20**-catalyzed reaction of 1-pentanethiol with 1-hexyne showed the empirical rate low expressed as rate $= k_{obs}$[**20**]^1[1-hexyne]^1[1-pentanethil]^x ($x = 1$ for $\leq$0.3 M and $x = 0$ for $\geq$0.3 M) with $\Delta H^{\ddagger} = +18.1(1.2)$ kcal mol^{-1} and $\Delta S^{\ddagger} = -20.9(2.5)$ e.u. In addition, a secondary kinetic isotope effect [$k_H/k_D = 1.3(0.1)$] was observed in the reaction of 1-pentanethiol with PhC≡C–D catalyzed by **20**. These and other findings are consistent with the catalytic cycle shown in Scheme 13, involving alkyne insertion into the Zr–SR bond (i), which is the turnover-limiting process, followed by protonolysis of Zr–C in **23** by thiol (ii).



(12)



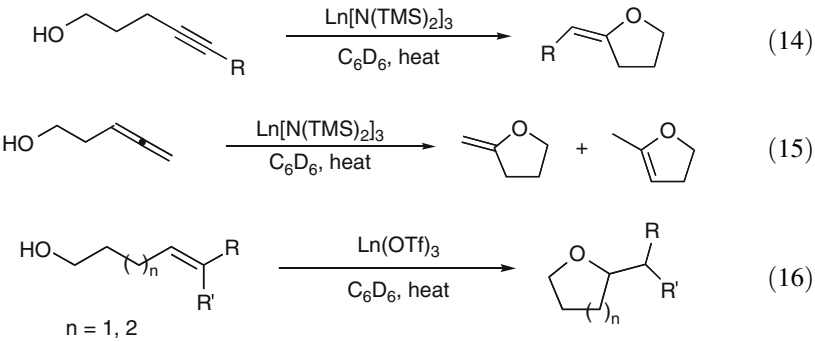
(13)



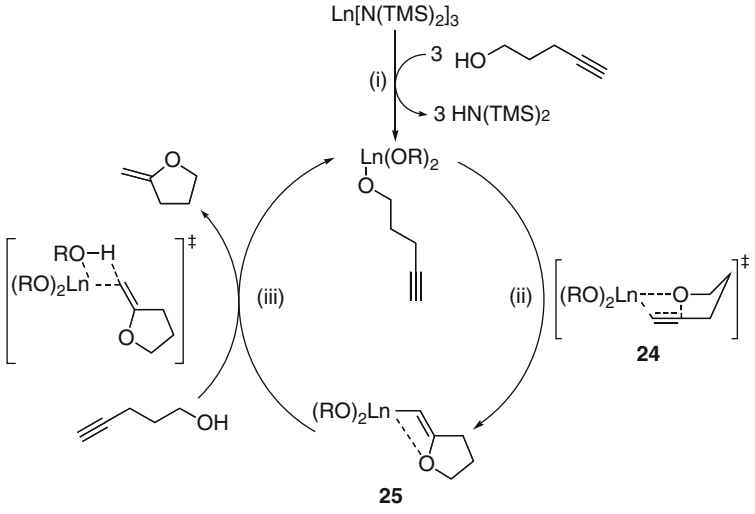
Scheme 13 Catalytic cycle for organozirconium(IV)-catalyzed hydrothiolation

2.2.3 Organolanthanide-Catalyzed Intramolecular Hydroalkoxylation

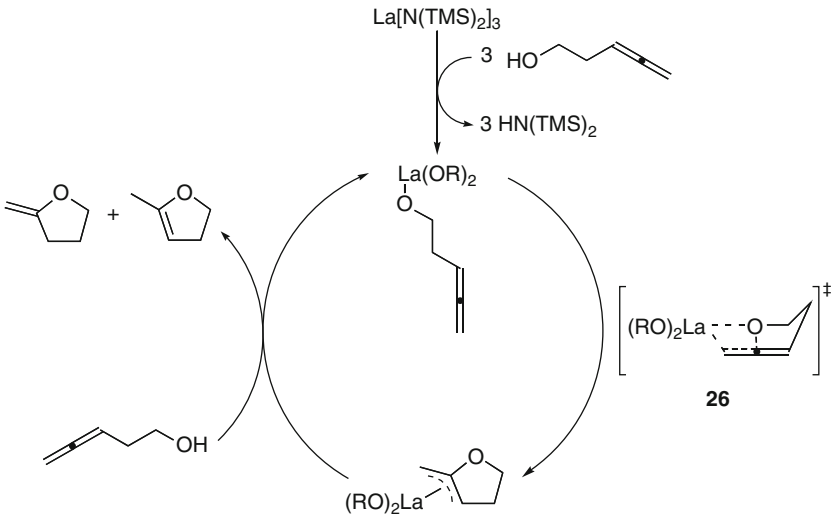
Marks and coworkers have reported the syntheses of oxygen-containing heterocycles by organolanthanide-catalyzed intramolecular hydroxyalkoxylation since 2007 (14)–(16) [36–41].



In the cyclization of γ-hydroxyalkynes [36–39], precatalyst, $Ln[N(TMS)_2]_3$ (Ln = La, Nd, Sm, Y, and Lu), is activated by alcohol-mediated protonolysis to give $Ln(OR)_3$ (Scheme 14, (i)), followed by intramolecular alkyne insertion (ii) that is the turnover-limiting process. The cyclization by alkyne hydroalkoxylation proceeds through π-complexation of the carbon–carbon triple bond [38] with high *exo* and *E*-selectivity as considered from the structure of the transition state **24**. Theoretical investigation was reported for this lanthanide-catalyzed cyclization, where a significant effect of metal ion size was obtained [38]. The activation parameters were $\Delta H^{\ddagger} = +20.2(1.0)$ kcal mol^{-1}, $\Delta S^{\ddagger} = -11.8(0.3)$ e.u., and $E_a = 20.9(0.3)$ kcal



Scheme 14 Catalytic cycle for $Ln[N(TMS)_2]_3$-catalyzed intramolecular hydroalkoxylation of γ-hydroxyalkyne (Ln = La, Nd, Sm, Y, and Lu)

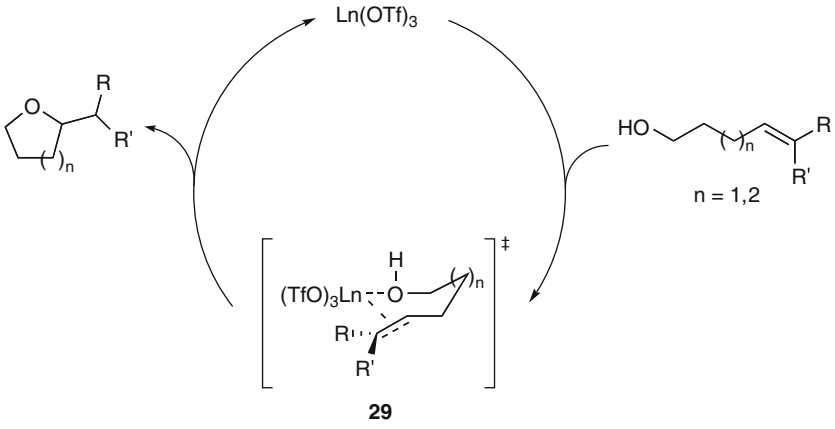


Scheme 15 Catalytic cycle for $La[N(TMS)_2]_3$-catalyzed intramolecular hydroalkoxylation of γ-hydroxyallene

mol^{-1} in the cyclization of $HO(CH_2)_3C{\equiv}CH$ with $La[N(TMS)_2]_3$ (40–80°C), indicating a highly-ordered transition state. The resulting cyclic vinyl ether **25** rapidly undergoes protonolysis by ROH (iii) to provide the product and the active catalyst. However, the structures of the active catalysts $Ln(OR)_3$ were not well-defined [42].

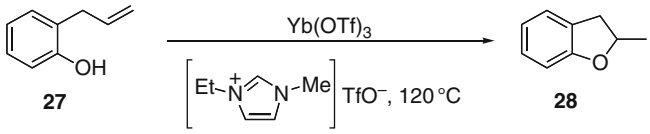
β-Hydroxy and γ-hydroxyallenes yield five-membered and six-membered rings, respectively, by $La[N(TMS)_2]_3$-catalyzed reactions [36]. As shown in Scheme 15, the addition of hydroxyl oxygen atoms takes place to the central allene carbon through **26**. The activity decreases compared with the case of hydroxyalkynes, which is explained in terms of the larger enthalpic barrier in the turnover-limiting process of the intramolecular insertion step [42]. A theoretical study by Tobisch [43] supports this mechanism and showed that reactive $La(OR)_3$ ($R = CH_2CH_2CH{=}C{=}CH_2$) undergoes energetically favorable coordination of ROH to form $La(OR)_3(ROH)_n$ (n = 1–6), where the forms having three η^1-RO ligands and those having one or two chelating η^2-RO ligands have almost similar stability in the range of 3.3 kcal mol^{-1}. Furthermore, the observed 5-*endo* cyclization ($\Delta G^{\ddagger}$ = 19.7 kcal mol^{-1}) is much more favorable than the unobserved 4-*exo* cyclization ($\Delta G^{\ddagger}$ = 37.5 kcal mol^{-1}) to give 2-vinyloxetane, and the 5-*endo* cyclization is followed by the protonolysis with the already coordinated ROH through a metathesis-like transition state ($\Delta G^{\ddagger}$ = ca. 10 kcal mol^{-1}).

Cyclization by hydroalkoxylation of γ- and δ-alkenols is achieved by lanthanide triflates as catalysts at 60–120°C in ion-liquids [40, 41]. In the cyclization of C_6H_4-*o*-$(OH)(CH_2CH{=}CH_2)$ **27** to **28** catalyzed by $Yb(OTf)_3$ in $[C_2mim][OTf]$ (17), the activation parameters were $\Delta H^{\ddagger}$ = +18.2(9) kcal mol^{-1}, $\Delta S^{\ddagger}$ = –17.0(1.4) e.u., and E_a = 18.2(8) kcal mol^{-1}, suggesting a highly organized transition state. A primary kinetic isotope effect of k_H/k_D = 2.48(9) was observed for the cyclization



Scheme 16 Catalytic cycle for $Ln(OTf)_3$-catalyzed intramolecular hydroalkoxylation of γ- and δ-alkenols (Ln = La, Nd, Sm, Yb, and Lu)

of CH_2=$CHCH_2CH_2CH_2OH$(D) catalyzed by $Yb(OTf_3)$ at 120°C, suggesting a catalytic pathway that involves kinetically significant intramolecular proton transfer. Proton scavenging experiments suggested the participation of an acidic proton in the catalytic cycle that originates from the hydroxy functionality. A free TfOH-catalyzed process as a major pathway was ruled out. An NMR study indicated hydroxyl and olefin coordination to Yb^{3+} (**29** in Scheme 16). Based on these experimental results, a catalytic cycle was proposed as shown in Scheme 16, which involves hydroxy and olefin activation by the electron-deficient Ln^{3+} center, followed by alkoxide nucleophilic attack with ring closure.



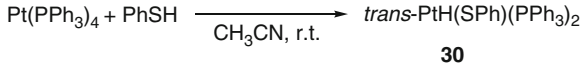
(17)

3 Type II Mechanism

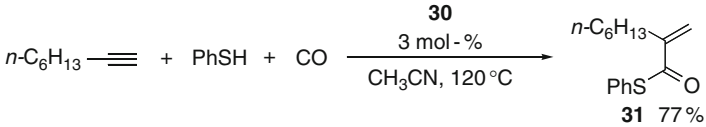
3.1 Pd(0) and Pt(0)-Catalyzed Hydroselenation of Alkynes

In 1992, when $Pt(PPh_3)_4$ was used instead of $Pd(OAc)_2$ [22], vinyl selenide **4**, derived from the Markovnikov-type product, was obtained as the major product in 80% yield. In this reaction, the generation of $PtH(SPh)(PPh_3)_2$ was considered. During the study on the hydrothiocarboxylation employing PhSH, 1-octyne, CO, and $Pt(PPh_3)_4$ as the catalyst [44], hydrido-thiolato Pt(II) complex **30** was isolated by the stoichiometric reaction of $Pt(PPh_3)_4$ with PhSH in acetonitrile at room

temperature (18). The complex was assigned as *trans*-PtH(SPh)(PPh_3)$_2$ (**30**) by ^{1}H NMR spectroscopic analysis [in $CDCl_3$: δ –10.01 (Pt–*H*, $J_{P–H}$ = 14 Hz, $J_{Pt–H}$ 961 Hz) [45]. The reaction of 1-octyne with PhSH and CO in the presence of 3 mol% of **30** gave the hydrothiocarboxylation product **31** in 77% yield (19).

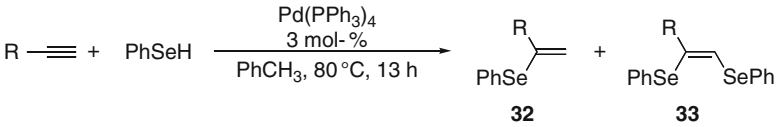


(18)



(19)

In 2003, Ananikov and Beletskaya and their coworkers proposed hydroselenation of terminal alkynes catalyzed by $Pd(PPh_3)_4$ and $Pt(PPh_3)_4$ [46]. In the case of $Pd(PPh_3)_4$, Markovnikov-type adducts **32** were obtained together with bis(selenide)s **33** (20).

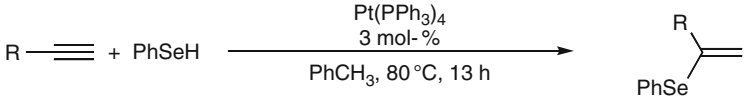


(20)

R = $HOCH_2$, Bu, Me_2NCH_2, *c*-C_6H_{10}(1-OH) 20%: 36% – 49%: 25%

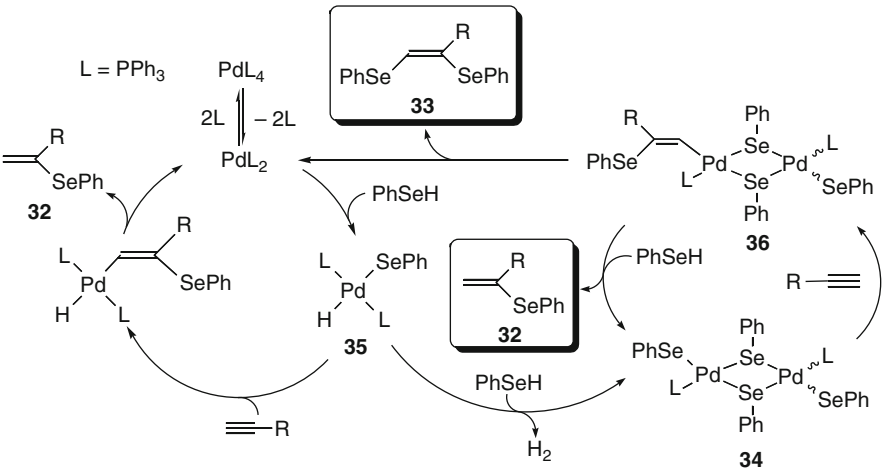
The reaction of $Pd(PPh_3)_4$ with PhSH took place rapidly with evolution of H_2, which was observed in ^{1}H NMR (δ 4.5). In the ^{31}P NMR, complexes assigned to dinuclear complexes *trans*- and *cis*-{Pd(SePh)(PPh_3)}$_2$(μ-SePh)$_2$ (**34**) at δ 28.2 and 26.8 in the relative ratio of 3:1. A mechanism involving both *trans*-PdH(SePh)(PPh_3)$_2$ (**35**) and dinuclear Pd(II) complexes **34** was proposed (Scheme 17). Two pathways are shown for the formation of vinyl selenide **32** there. Although they did not rule out the alternative pathway completely [3], Beletskaya and Ananikov proposed that the dominating pathway was protonolysis of selenovinyl Pd_2 complex **36** by PhSeH, based on observations: (1) hydrido Pd complex **35** was not observed in NMR experiments and (2) the reaction of HC≡CCH_2OH with a mixture of dinuclear Pd(II) complexes **34** in the presence of CF_3CO_2H yielded both bis(selenide) **33** (31%) and Markovnikov-type product **32** (15%).

On the other hand, the hydroselenation catalyzed by $Pt(PPh_3)_4$ provided only Markovnikov-type product **32** (21) [46].

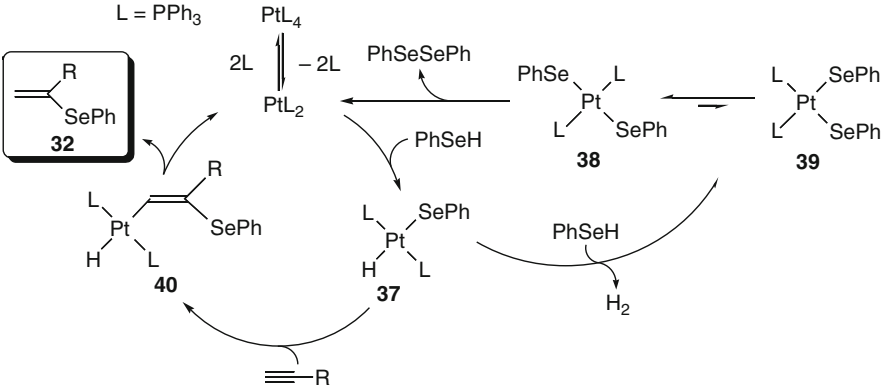


(21)

R = $HOCH_2$, Bu, Me_2NCH_2, *c*-C_6H_{10} (1-OH) 51% – 60%

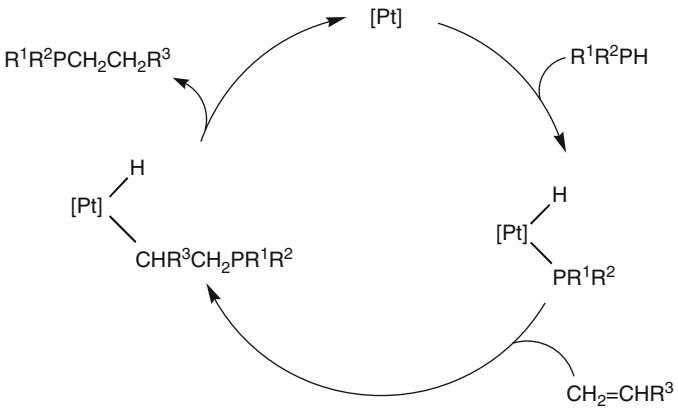


Scheme 17 Catalytic cycle for $Pd(PPh_3)_4$-catalyzed hydroselenation



Scheme 18 Catalytic cycle for $Pt(PPh_3)_4$-catalyzed hydroselenation

A key intermediate, *trans*-PtH(SePh)$(PPh_3)_2$ (**37**), was observed by ^{1}H NMR spectroscopy in the reaction of PhSeH with $Pt(PPh_3)_4$ in C_6D_6 (Pt–*H*: δ –8.77, $J_{Pt–H}$ 999.8 Hz, and $J_{Se–H}$ = 44.1 Hz). In ^{31}P NMR, signals assigned to *trans*- and *cis*-Pt$(SePh)_2(PPh_3)_2$ (**38** and **39**) were observed at δ 20.8 ($J_{Pt–P}$ = 2,842 Hz) and δ 18.5 ($J_{Pt–P}$ = 2,966 Hz), respectively, along with minor signals at δ 20.8, 23.7, and 30.6. *cis*-Pt$(SePh)_2(PPh_3)_2$ (**39**) very rapidly isomerized to *trans*-Pt$(SePh)_2(PPh_3)_2$ (**38**) at 80°C. Thus, a catalytic cycle shown in Scheme 18 was proposed [46]. Hydrido Pt (II) complex **37** undergoes insertion of alkyne into the Pt–Se bond to give *syn*-selenoplatination intermediate **40**, the reductive elimination from which yields the vinyl selenide **32** and $Pt(PPh_3)_2$. Incidentally, in a review [3], Beletskaya and Ananikov mentioned that the isomerization from *trans* to *cis* geometry of hydrido-(2-selenovinyl) Pt(II) complex **40** may be required for C–H reductive elimination.



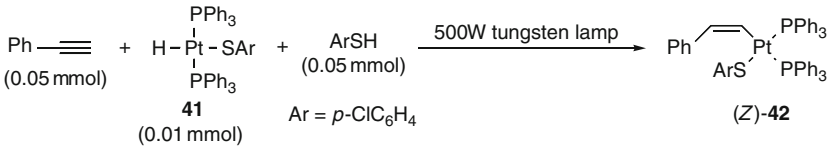
Scheme 19 Catalytic cycle for $Pt[P(CH_2CH_2CN)_3]_3$-catalyzed hydrophosphination

Importantly, while the reaction of PhSeH with 1-hexyne in the presence of *trans*-$Pt(SePh)_2(PPh_3)_2$ (**38**) gave $H_2C{=}C(SePh)Bu$ in 60% yield, the reaction of $HC{\equiv}CCH_2OH$ with **38** *in the presence of* CF_3CO_2H gave *only a trace amount (~0.5%) of* $H_2C{=}C(SePh)CH_2OH$. The latter result is quite in contrast with the case of the catalytic reaction with dinuclear Pd(II) complexes **34** (*vide supra*), ruling out the pathways involving protonolysis of vinyl Pt(II) intermediate **40** with acid.

In relation, Pringle and coworkers reported the reaction of PH_3 with acrylonitrile catalyzed by $Pt[P(CH_2CH_2CN)_3]_3$ to yield $P(CH_2CH_2CN)_3$ [47]. They proposed that the reaction proceeds through oxidative addition of the P–H followed by insertion of acrylonitrile into the Pt–P bond (not Pt–H) bond and a C–H reductive elimination (Scheme 19) [45].

3.2 Stoichiometric Reaction of Hydrido-Chalcogenolato Pt(II) Complexes with Alkynes

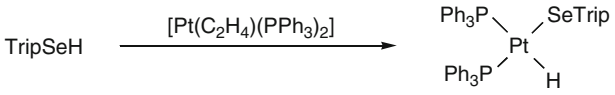
Kuniyasu and Kurosawa reported that, while hydrido-thiolato Pt(II) complex, *trans*-$PtH(SC_6H_4$-*p*-$Cl)(PPh_3)_2$ (**41**), did not react with phenylacetylene in C_6D_6 at room temperature, **41** did react with phenylacetylene *in the presence of p-*ClC_6H_4SH *under photoirradiation* to furnish (*Z*)-**42** in 77% yield (*cis*/*trans* = 73/27) in C_6D_6 or 85% yield (*cis*/*trans* = 85/15) in acetone-d_6 (22) [48]. In this reaction, (*Z*)-**42** is the kinetic product and the insertion of phenylacetylene to the Pt–H bond occurs in a *trans*-fashion (*anti*-addition). The reaction of phenylacetylene with **41** in the presence of AIBN and *p*-ClC_6H_4SH gave (*Z*)-**42** in 77% yield. *trans*-$PtH(X)(PPh_3)_2$ (X = Cl, Br, and I) also lead to similar reactions under photoirradiation or in the presence of AIBN to furnish the corresponding (*Z*)-insertion products. Although a pivotal role of thiyl radical is considered in this *trans*-insertion, the mechanism remains unclear.



(22)

In the case of dithiolato Pt(II) complex, *trans*-$Pt(SAr)_2(PPh_3)_2$, Kuniyasu and Kambe succeeded in the observation of stepwise double insertion of terminal alkynes followed by reductive elimination to give (*Z*,*Z*)-1,4-diarylthio-1,4-disubstituted-1,3-butadienes [49, 50]. They also obtained (2-chalcogenovinyl)-selenolato Pt(II) [51] and Pd(II) complexes [52] by other methods.

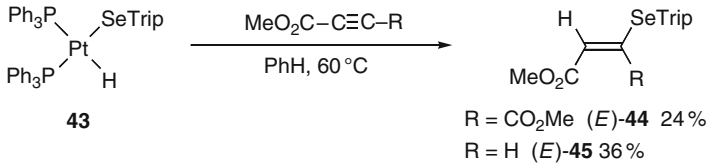
Ishii and coworkers investigated stoichiometric reaction of hydrido-selenolato Pt(II) complexes, *cis*-PtH(SeTrip)$(PPh_3)_2$ (**43**) (Trip = 9-triptycyl), with alkynes [53]. The hydrido-selenolato Pt(II) complex **43** is obtained by the reaction of TripSeH with $Pt(C_2H_4)(PPh_3)_2$ (23) [54].



43

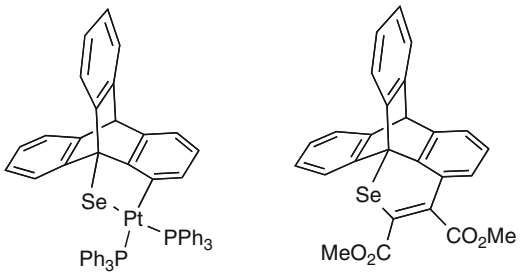
(23)

The reaction of **43** with activated alkynes, dimethyl acetylenedicarboxylate (DMAD), or methyl propiolate (MP), in benzene at 60°C, gave *syn*-adducts (*E*)-**44** and (*E*)-**45** in 24% or 36% yield, respectively, together with byproducts, selenaplatinacycle **46**, 1*H*-2-benzoselenin derivative **47** (in the case of DMAD), $(TripSe)_2$, and $[Pt(alkyne)(Ph_3P)_2]$ (alkyne = DMAD or MP) (24). The selenaplatinacycle **46** is a thermal reaction product of **43** as observed in other hydrido-selenolato Pt(II) [55–57], hydrido-thiolato Pt(II) [58], and hydrido-selenolato Pd(II) [59] complexes. 1*H*-2-Benzoselenin **47** is a carboselenation product of DMAD with **46** or TripSeH [53].



43

R = CO_2Me (*E*)-**44** 24%
R = H (*E*)-**45** 36%

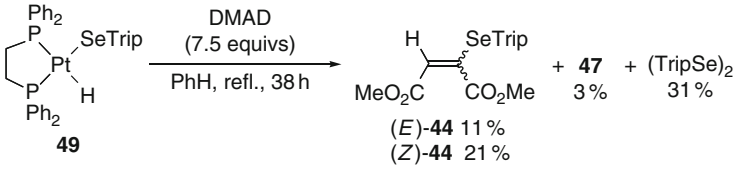


46 **47**

(24)

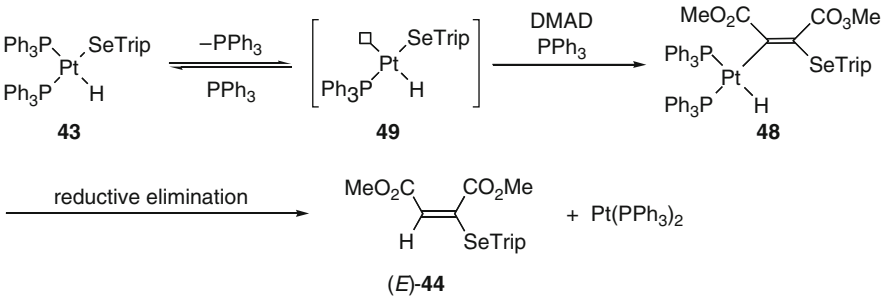
This result is in contrast with the report by Ananikov and Beletskaya on the reaction of PhSeH with methyl propiolate in the presence of $Pt(PPh_3)_4$ in toluene at 80°C to give a 1:7 mixture of the corresponding (*E*)- and (*Z*)-vinyl selenide ($PhSCH{=}CHCO_2Me$) by a non-catalytic reaction [46]. The reaction of *cis*-PtH(SeTrip)$(PPh_3)_2$ (**43**) with 1-hexyne, phenylacetylene, diphenylacetylene, or methyl 2-butynoate did not yield hydroselenation adducts, which is probably due to the steric hindrance of the bulky 9-triptycyl group and strong coordination ability of this alkaneselenolato ligand compared with benzeneselenolato ligand.

The regio- and stereoselective formation of (*E*)-**44** and (*E*)-**45** supports the *syn*-insertion of DMAD or MP into the Pt–Se bond of **43** to give (*Z*)-2-selenovinyl Pt(II) complex (**48** in Scheme 20), followed by reductive elimination. On the other hand, the reaction of PtH(SeTrip)(dppe) (**49**) [dppe = 1,2-bis(diphenylphosphino)ethane] with DMAD in benzene was sluggish at 60°C, and heating in refluxing benzene for 38 h was necessary for complete consumption of **49** to yield (*E*)-**44** (11%), (*Z*)-**44** (21%), 1*H*-2-benzoselenin **47** (3%), and $(TripSe)_2$ (31%) (23). These products are considered to be formed by the reaction of TripSeH, generated by reductive elimination of **49**, with DMAD.



(25)

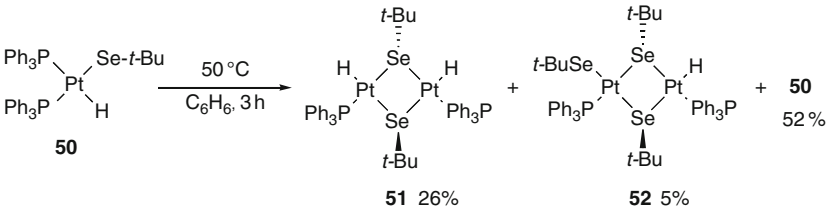
The difference between *cis*-PtH(SeTrip)$(PPh_3)_2$ (**43**) and PtH(SeTrip)(dppe) (**49**) in the reactivity toward DMAD is attributed to the weaker coordination ability of PPh_3 than that of dppe, that is, the dissociation of one phosphine ligand (PPh_3) from **43** is essential for the hydroselenation reaction. The reaction of **43** with DMAD in the presence of additional PPh_3 (2 molar equiv) to impede the formation (*E*)-**44** and to give $(TripSe)_2$ (39%), **43** (35%), and $Pt(dmad)(PPh_3)_2$ (53%). Thus, as depicted in Scheme 20, dissociation of one of the PPh_3 ligands from **43** occurs first to give coordination-unsaturated intermediate **49**, where the ligand *trans* to H would be



Scheme 20 Formation mechanism of *syn*-adduct (*E*)-**44** by the reaction of *cis*-PtH(SeTrip)$(PPh_3)_2$ (**43**) with DMAD

detached owing to the stronger *trans* effect of the H than that of the selenolato ligand. Then, **49** undergoes insertion of DMAD and re-coordination of PPh_3 to yield hydrido-(2-selenoalkenyl) Pt(II) intermediate **48**, from which reductive elimination provides the *syn*-adduct (*E*)-**44** and $Pt(PPh_3)_2$. Similar prior dissociation of a phosphine ligand was reported for the insertion of an alkyne into the Pt–S bond in *trans*-$Pt(SAr)_2(PPh_3)_2$ [49, 50]. *cis*-$PtH(SeTrip)(PPh_3)_2$ (**43**) did not work as the catalyst for the reaction of TripSeH with DMAD because it would undergo coordination of DMAD preferentially furnishing $Pt(dmad)(Ph_3P)_2$ persistent under the conditions.

cis-$PtH(Se\text{-}t\text{-}Bu)(PPh_3)_2$ (**50**) is an alternative isolable hydrido-alkaneselenolato complex, which is stable at room temperature in the absence of air and moisture [60]. Heating **50** in benzene at 50°C, two dinuclear hydrido Pt(II) complexes **51** and **52** were formed (26). The stoichiometric reaction of **50** with methyl propiolate gave a mixture of (*E*)- and (*Z*)-adducts in 28% and 6% yields, respectively, which are probably produced by the reaction of *t*-BuSeH, formed by the reductive elimination of **50**, with methyl propiolate. This low reactivity of **50** toward alkynes is similar to that of *cis*-$PtH(SeTrip)(PPh_3)_2$ (**43**) as mentioned above. The reactions of the two dinuclear hydrido Pt(II) complexes with methyl propiolate gave complex mixtures.

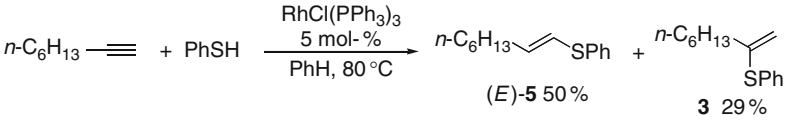


(26)

3.3 *Hybrid Type of Type I and Type II Mechanisms: Rh(I) and Ir(I) Complex-Catalyzed Hydrothiolation*

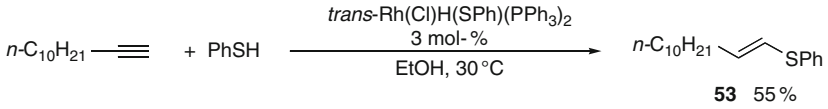
3.3.1 $RhCl(PPh_3)_3$-Catalyzed Hydrothiolation

The addition of PhSH to 1-octyne catalyzed by $RhCl(PPh_3)_3$ (Wilkinson catalyst) gives (*E*)-**5** (*anti*-Markovnikov adduct) as the main product together with **3** (27) [24]. The reaction carried out in EtOH provided the highest product selectivity [(*E*)-**5** 58%; **3** 0%]. When the reaction in EtOH was examined in the presence of galvinoxyl as a radical inhibitor, only (*E*)-**5** was formed in 73% yield, suggesting that a non-radical mechanism is operative for the formation of (*E*)-**5**.



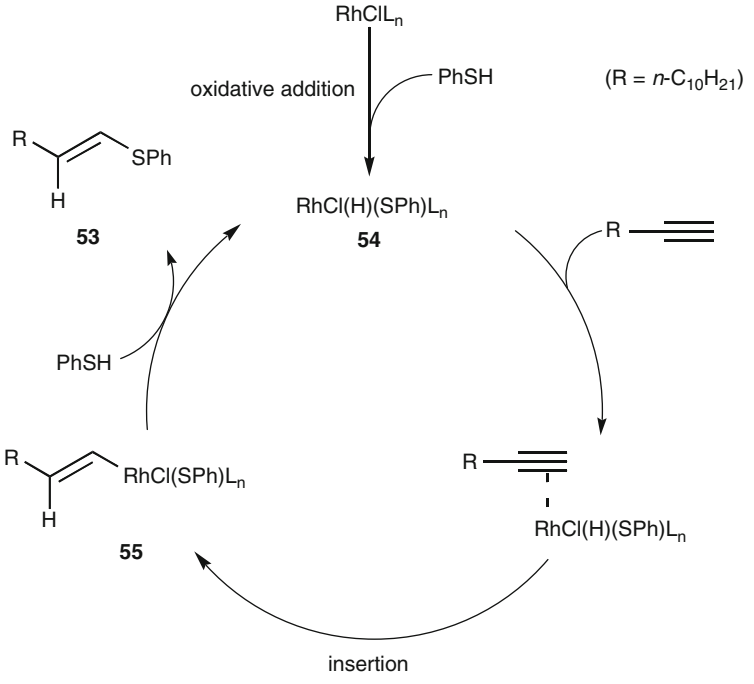
(27)

The stoichiometric reaction of $RhCl(PPh_3)_3$ with PhSH in dichloromethane at 20°C under argon atmosphere gave a hydrido-thiolato complex, *trans*-Rh(Cl)H(SPh)$(PPh_3)_2$ [61]. The reaction of PhSH with 1-dodecyne in the presence of *trans*-Rh(Cl)H(SPh)$(PPh_3)_2$ as the catalyst (3 mol%) gave **53** in 55% yield (26).



(28)

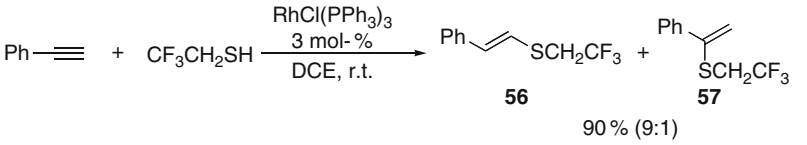
The proposed mechanism is shown in Scheme 21, where hydrido-thiolato Rh (III) complex **54** undergoes the stereoselective insertion of alkynes into the Rh–H bond to form the *trans*-vinyl Rh(III) complex **55** and the following reductive elimination of the complex in the presence of excess PhSH yields *anti*-Markovnikov-type, *syn*-adducts **53** and **54**. This catalytic cycle is based on the ^1H NMR observations. Thus, the ^1H NMR spectrum of a stoichiometric mixture of *trans*-Rh(Cl)H(SPh)$(PPh_3)_2$ with 1-dodecyne exhibited a doublet δ 5.1, probably due to a vinylic proton of *trans*-vinylrhodium intermediate (corresponding to **55**) with disappearance of signals due to Rh–*H* (δ –16.4) and *n*-$C_{10}H_{21}C{\equiv}C$–*H*. This doublet disappeared by the addition of PhSH giving the vinylic sulfide **53** after 6 h at room temperature. This observation supports that the insertion of alkynes occurs to the Rh–H bond and not to Rh–S bond of *trans*-Rh(Cl)H(SPh)$(PPh_3)_2$ and that the



Scheme 21 Catalytic cycle for $RhCl(PPh_3)_3$-catalyzed hydrothiolation of alkynes to give the *anti*-Markovnikov-type product

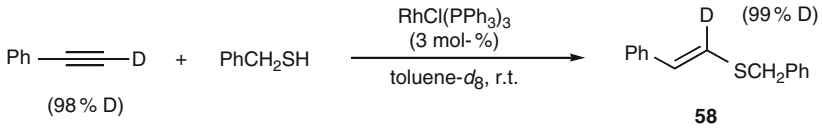
final product is produced not by a sole reductive elimination of *trans*-vinylrhodium intermediate **55** but by a *PhSH-assisted* reductive elimination.

In 2007, Love and coworkers reported the hydrothiolation of alkynes with alkanethiol using $RhCl(PPh_3)_3$ [62]. Under optimized conditions (in 1,2-dichloroethane at room temperature), the reaction of CF_3CH_2SH with phenylacetylene in the presence of 3 mol% of $RhCl(PPh_3)_3$ furnished *anti*-Markovnikov (**56**) and Markovnikov (**57**) adducts in a ratio of 9:1 in 90% yield (27), the regioselectivity of which is similar to the case of PhSH [see (28)].



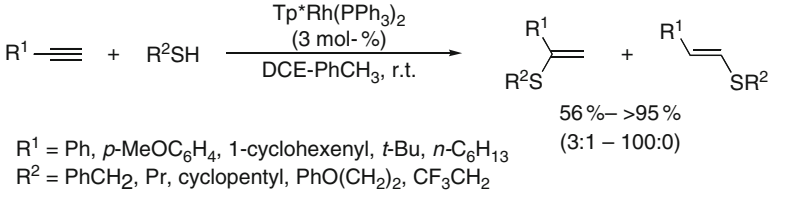
(29)

In the reaction employing deuterium-labeled phenylacetylene (PhC≡CD), only *syn*-addition product **58** was obtained (30), excluding the vinylidene pathway. Love suggested that the reactions involve alkyne insertion into the Rh–H bond of the intermediate, formed by oxidative addition of thiol to $RhCl(PPh_3)_3$, from steric reason.

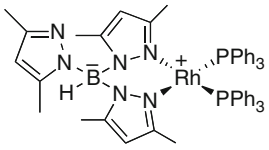


(30)

Love also reported $Tp^*Rh(PPh_3)_2$-catalyzed hydrothiolation of alkanethiol to alkynes (31) [63–65], in which the regioselectivity was opposite of that obtained with other Rh(I) catalysts mentioned above. In the reaction of arenethiols (ArSH: Ar = Ph, *p*-Tol, *p*-BrC_6H_4) with Ar′C≡CH (Ar′ = Ph, *p*-$MeOC_6H_4$, and *o*, *p*-$F_2C_6H_3$), the selectivity is lowered (1.4:1 to 6:1) [63].



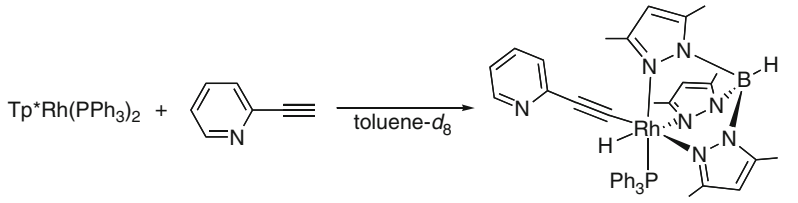
(31)



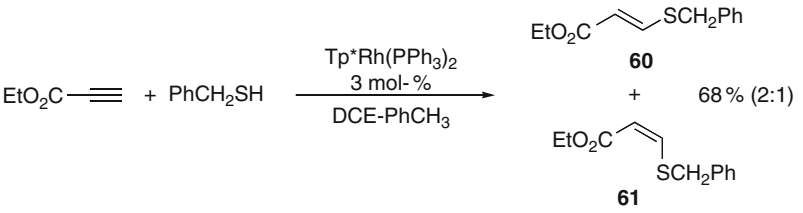
$Tp^*Rh(PPh_3)_2$

While the reactions of $PhCH_2SH$ with *para*-substituted phenylacetylenes (Ar′C≡CH) in the presence of $Tp^*Rh(PPh_3)_2$ provided Markovnikov-type adducts

$PhCH_2S(Ar')C{=}CH_2$ regioselectively in moderate to high yields, 2-pyridylacetylene was unreactive in hydrothiolation [66]. The stoichiometric reaction of $Tp^*Rh(PPh_3)_2$ with 2-pyridylacetylene in toluene-d_8 was investigated to reveal the formation of acetylido-hydrido complex **59** (32), the formation of which is rapid and irreversible to preclude the reaction of thiol with $Tp^*Rh(PPh_3)_2$. The reaction of $PhCH_2SH$ with ethyl propiolate catalyzed by $Tp^*Rh(PPh_3)_2$ yielded **60** and **61** in the ratio of 2:1 (33).



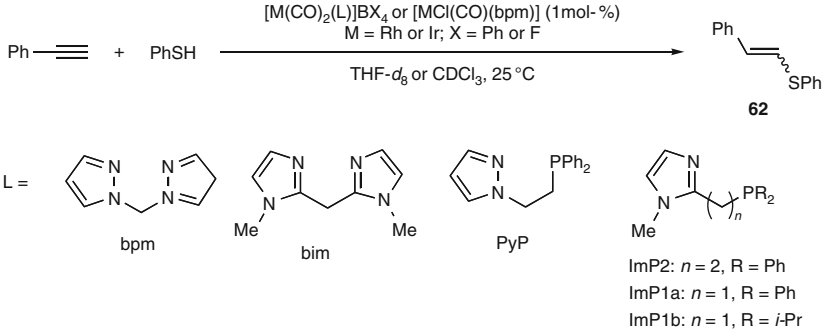
(32)



(33)

3.3.2 Cationic Rh(I) and Ir(I) Complex-Catalyzed Hydrothiolation

Hydrothiolation with cationic ($[M(CO)_2(L)]BX_4$; L = N,N and N,P bidentate ligands; bim, PyP, bpm, ImP2, ImP1a, IMP1b; X = Ph, F) or neutral ([MCl(CO)(bpm)]) Rh(I) and Ir(I) complexes as the catalysts were reported by Messerle and coworkers (34) [67, 68]. The catalytic reaction gave a mixture of (*E*)- and (*Z*)-*anti*-Markovnikov adducts **62** as the main products. Monitoring the course of the reaction by ^1H NMR showed that the (*Z*)-isomer was the kinetic product [67]. Although mechanism was not shown in the literatures, a mechanism similar to the cases of neutral Rh(I) and Ir(I) complexes described above may be operative.



(34)

4 Conclusion

Since the first reports of Pd(II)-catalyzed hydroselenation and hydrothiolation 1992, considerable investigations have accumulated experimental evidence for the mechanism, in particular for Type I mechanism. Each step of Type I mechanism, structures of active catalysts, the reaction of alkynes with the active catalysts, and the protonolysis of the resulting vinyl metal complexes, has been verified for Pd, Ni, Zr, Ln, and An-catalyzed hydrochalcogenations by isolation of intermediates, isotope-labeled experiments, and kinetic studies. With regard to Type II mechanism, while the initial oxidative addition of REH (E = S, Se) to a low-valent transition metal catalyst (metal = Pd and Pt) has been verified by direct (for Pt) or indirect (for Pd) experimental evidence, the following steps of alkyne insertion to chalcogenolate-hydrido complex and reductive elimination of resultant vinyl metal complexes leave room for further mechanistic investigations to obtain direct evidence. On the other hand, a hybrid mechanism of Type I and Type II has been clarified for the hydrothiolation with Rh(I) complexes.

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Early Transition Metal (Group 3–5, Lanthanides and Actinides) and Main Group Metal (Group 1, 2, and 13) Catalyzed Hydroamination

Alexander L. Reznichenko and Kai C. Hultzsch

Abstract The hydroamination of alkenes, dienes, allenes, and alkynes by early transition metal catalysts has seen significant progress over the last decade, especially with respect to control of regio- and stereoselectivity and the synthesis of more complex nitrogen-containing skeletons. This article provides an overview over the application of catalyst systems based on the 17 rare earth elements, as well as group 4 and group 5 metals. These electropositive metal catalysts operate via activation of the amine to form catalytic active metal-amido or metal-imido species, although the true nature of this species is not known with certainty for all systems and may vary for different substrate classes. This mode of activation differentiates early transition metal catalysts from many late transition metal catalysts that operate via activation of the unsaturated C–C linkage (alkene, 1,3-diene, allene, or alkyne). Alkali metals, alkaline earth metals and aluminum are included in this overview as well, as they show strong similarities in their reactivity and mechanistic pathways to aforementioned early transition metals. While the structure-reactivity principles are well understood for certain hydroamination processes, e.g., in the intramolecular hydroamination of aminoalkenes or the intermolecular hydroamination of alkynes, other transformations, in particular the intermolecular hydroamination of alkenes, remain highly challenging. Due to the potential of the hydroamination process for the synthesis of pharmaceuticals and other industrially relevant fine chemicals, a strong emphasis is given on the application of chiral catalysts in stereoselective processes.

Keywords Alkali metals · Alkaline earth metals · Aluminum · Asymmetric synthesis · Catalysis · Group 4 metals · Group 5 metals · Hydroamination · Rare earth metals

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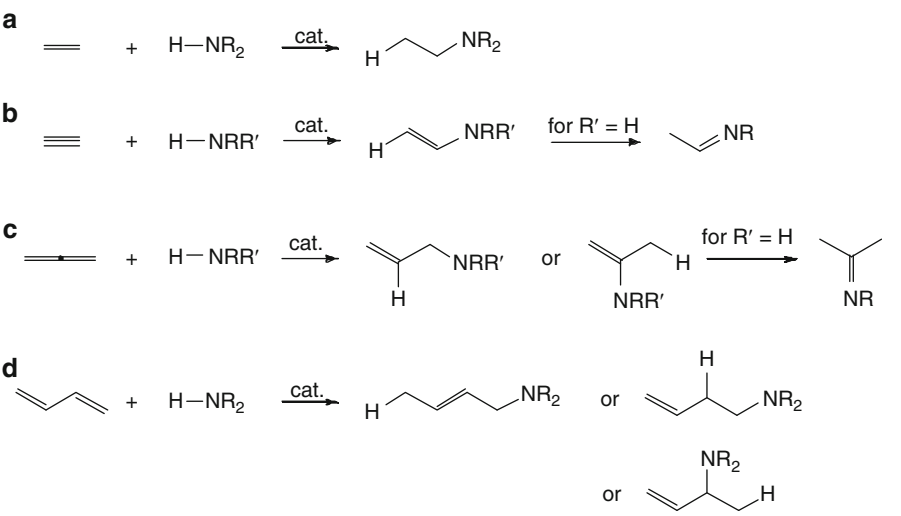
1 Introduction: General Features

The addition of an amine N–H bond across an unsaturated carbon–carbon linkage, the so-called hydroamination, allows a facile and highly atom-economical access to industrially relevant nitrogen-containing basic and fine chemicals as well as naturally occurring alkaloid skeletons [1–6]. Significant research efforts over the last two decades have led to the elucidation of novel powerful catalysts based on various main group and transition metals for the hydroamination of alkenes, alkynes, allenes, and dienes (Scheme 1) to form amines, imines, and enamines with diverse topologies in an inter- and intramolecular fashion.

This chapter will cover the development of catalysts based on main group metals (alkali and alkaline earth metals, as well as aluminum) and early transition metals (groups 3–5, as well as lanthanides and actinides). Complexes of the rare earth metals (comprising of group 3 metals and the lanthanides) and group 4 metals belong to the most intensively studied and most active and selective catalyst systems for the hydroamination reaction. While alkali metal catalysts have been known for a long time [7], catalyst systems based on alkaline earth metals and aluminum have been introduced only recently and studied less extensively.

Several important features are common for all catalysts described in this chapter. First, the metals covered are highly electrophilic and "hard" binding partners typically operating via activation of the *amine* rather than via activation of the *alkene* (or other unsaturation, e.g., diene, allene, or alkyne moiety), as the early transition metals lack *d* electrons for effective π-backbonding. Metal-carbon



Scheme 1 The catalytic hydroamination of alkenes (**a**), alkynes (**b**), allenes (**c**), and dienes (**d**) leads to amines, imines, and enamines. The reactions may also be performed in an intramolecular fashion (not shown)

σ-bonds of early transition metals (as well as alkali and alkaline earth metals) are typically very reactive and short lived, contrary to late transition metals. An additional consequence is the high basicity of some of the complexes (in particular that of alkali and alkaline earth metals), which might result in unexpected side reactions such as alkene isomerization or hydroaminoalkylation. Last but not least, the high electrophilicity and basicity of the complexes makes them generally rather air and moisture sensitive, which requires the use of inert atmosphere techniques, dry solvents, and certainly limits the number of tolerated functional groups.

Rare earth metal and main group metal catalysts share similar reaction mechanisms involving the insertion of the unsaturated C–C bond into a metal-amide bond, which is sometimes referred to as the "lanthanide-like" mechanism. Group 4 (and potentially also group 5) metal catalysts predominantly operate via a mechanism involving a [2 + 2]-cycloaddition of the unsaturated C–C moiety to a metal-imido species, also in some cases it has been proposed that also a lanthanide-like mechanism may be operational. A similar chameleon-like behavior has been found for actinide catalysts, which have been postulated to operate via a lanthanide-like mechanism for reactions involving alkenes, while a metal-imido [2 + 2]-cycloaddition mechanism was suggested for reactions involving alkyne substrates.

Multiple efficient catalysts were reported for the intramolecular process, while the intermolecular process has been studied predominantly for alkynes. The reactivity of the unsaturated fragment decreases in the order alkyne $>$ allene $\sim$ diene $>$ vinyl arene $\gg$ unactivated alkene with the intermolecular hydroamination of simple alkenes representing the most difficult transformation. The hydroamination of all types of carbon–carbon unsaturated fragments will be covered in this chapter.

Although hydroamination reactions are regiospecific in most cases, the stereoselective synthesis of pharmaceutically relevant chiral amines via hydroamination remains challenging despite significant progress for asymmetric intramolecular reactions and some initial reports on asymmetric intermolecular hydroamination. Selected examples of asymmetric hydroamination will be covered in this chapter due to the volume limitations, and the reader should refer to available specialized reviews for a more comprehensive coverage of the stereoselective aspects [8–15].

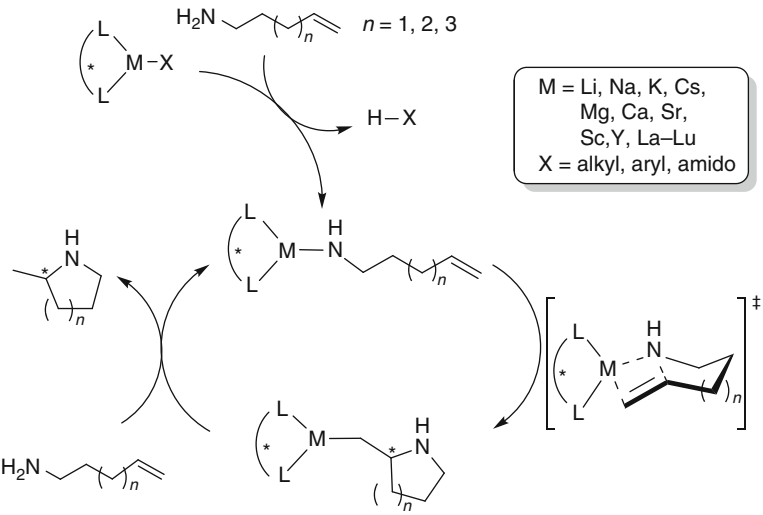
2 Mechanisms

Contrary to late transition metals, polar organometallic catalysts do not exhibit a significant degree of mechanistic diversity. The metals involved are in the d^0 state, so neither oxidative addition nor reductive elimination is feasible. Instead, the mechanisms involve insertion steps, cycloadditions, and ligand redistributions via σ-bond metathesis during which the oxidation state of the metal does not change. Two general mechanisms are being discussed for main group and early transition metals.

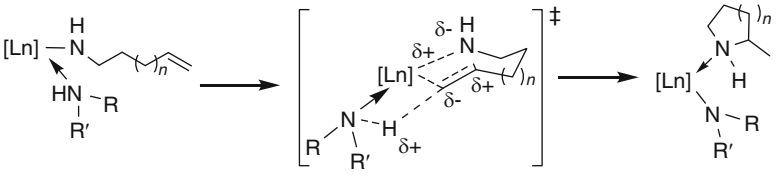
2.1 Insertion Mechanism

The insertion pathway was established via experimental [16–18] and theoretical [19] studies on rare earth metal catalyzed hydroamination/cyclization of aminoalkenes. It is believed to proceed through a metal amido species, which is formed upon protonolysis of a metal amido or alkyl bond (Scheme 2). The first step of the catalytic cycle involves insertion of the alkene into the metal amido bond with a seven-membered chair-like transition state (for $n = 1$). The roughly thermoneutral [17, 19] insertion step is considered to be rate determining, giving rise to a zero-order rate dependence on substrate concentration and first-order rate dependence on catalyst concentration. Although the protonolysis step is considered to be fast, a strong primary isotope effect as well as an effect of the isotope substitution on diastereoselectivity [17] have been observed, which is indicative of a significant N–H bond disruption in the transition state of the rate-determining alkene insertion step. A plausible explanation involves partial proton transfer from a coordinated amine to the α-carbon in the four-membered insertion transition state (Scheme 3).

However, some experimental data, in particular the observation of sequential hydroamination/bicyclization sequences (see Sect. 4) catalyzed by organolanthanide [20–23] and organolithium [24] species is in conflict with this scenario, as the sequential reaction requires a finite lifetime for the rare earth metal alkyl intermediate. Therefore, the intermediacy of the metal-alkyl species and its potential lifetime is unclear at present and probably strongly depends on catalyst and substrate structure. Unfortunately, involvement of concerted insertion/protonolysis



Scheme 2 Insertion mechanism for the hydroamination/cyclization using aminoalkene substrates as an example



Scheme 3 Proposed concerted protonolysis/insertion *via* free amine-assisted alkene insertion in hydroamination/cyclization (RR´NH = substrate or hydroamination product) [17]

pathway in a catalytic cycle has only been addressed computationally for aminoallenes [25] and aminodienes [26]. Although classical stepwise insertion/protonolysis was found to be more energetically accessible, a concerted process might also contribute depending on the spatial demands around the rare earth metal center.

The resting state of the catalyst is believed to be an amine adduct of the catalytic active metal–amide of the type $Cp^*_2Ln(NHR)(NH_2R)$, which has been spectroscopically and crystallographically characterized for the lanthanocene catalysts [17]. Amines, coordinating solvents, and other external bases may adversely affect the reactivity of the rare earth metal center, in particular if the metal center is readily accessible.

The intramolecular hydroamination reaction of aminoalkenes and other substrates involves two key steps in the catalytic cycle. Although the insertion step is generally perceived as the rate-determining step of the process, this may not be true for all substrate classes. The hydroamination/cyclization of aminoalkenes differs significantly from reactions involving aminoalkynes, aminoallenes, and conjugated aminodienes from a thermodynamic point of view. The alkene insertion step of the

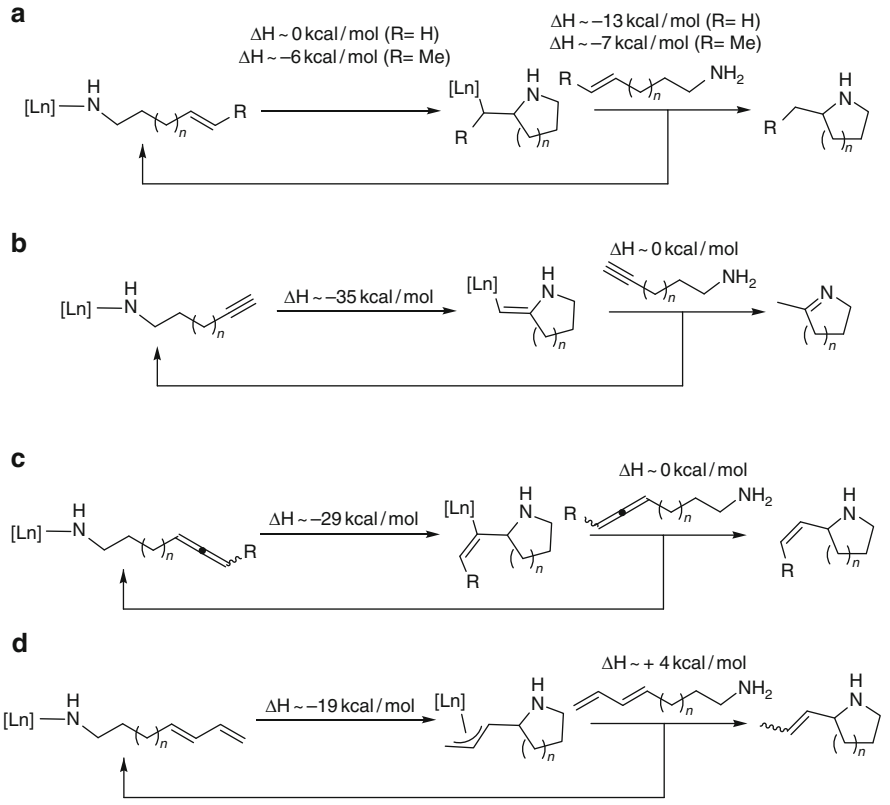


Fig. 1 Thermodynamics of the elementary steps in rare earth metal-catalyzed hydroamination/cyclizations [17, 27–31]

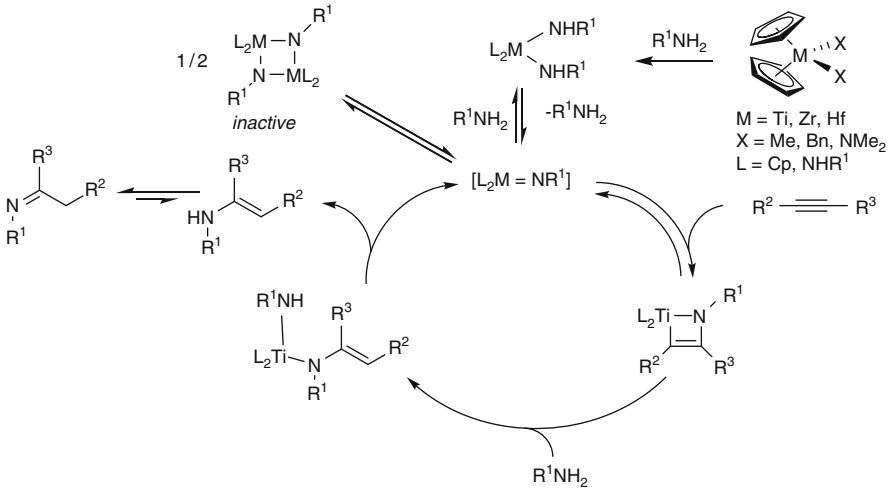
Ln-amide into the carbon–carbon double bond is approximately thermoneutral for terminal aminoalkenes and it is only slightly exothermic for an internal aminoalkene with a 1,2-disubstituted alkene (Fig. 1a) [17, 27]. The subsequent protonolysis of the primary rare earth metal alkyl species is quite exothermic, to a lesser extent also for the secondary rare earth metal alkyl species. In marked contrast, insertion of an alkyne, allene, or 1,3-diene into the Ln-amide bond is very exothermic (Fig. 1b–d) [28–31]. Protonolysis of the resulting vinyl (in case of alkynes and allenes) or η^3-allyl (in case of conjugated dienes) rare earth metal species is about thermoneutral (for the vinylic species) to slightly endothermic (for the allylic species) due to the significant stabilization of these species. Despite these significant differences, it has been proposed that in all these cyclization reactions the insertion step is rate determining [19, 32], followed by a rapid protonolysis step. However, recent DFT analyses of the catalytic cycle of the rare earth metal-catalyzed hydroamination of dienes and allenes suggest that protonolysis of the rare earth metal η^3-allyl species (in the hydroamination of dienes), respectively vinylic species (in the hydroamination of allenes), is the rate-determining step [33, 34].

A mechanism similar to that of the rare earth metals was proposed for the hydroamination/cyclization of aminoalkenes using alkali metals [35], alkaline earth metals [36], and aluminum [37], although much less kinetic and mechanistic data is available in these cases. Some experimental evidence for a concerted insertion and protonolysis step for certain magnesium catalysts has been obtained recently [38, 39].

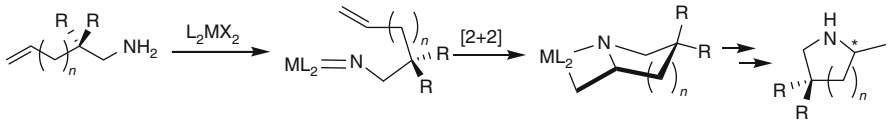
The intermolecular hydroamination is significantly less feasible than the intramolecular process as the C–C unsaturated moiety is not tethered in the vicinity of the catalytic center. The mechanism is believed to be analogous to the intramolecular case, with insertion being less favorable [20]. The insertion step was identified to be rate limiting in the intermolecular lithium-amide–catalyzed hydroamination of vinyl arenes by detailed DFT-analysis [40].

2.2 *Imido Mechanism*

The mechanism of the group 4 metal-catalyzed hydroamination of alkynes (Scheme 4) and allenes has been thoroughly investigated in detailed kinetic and mechanistic [41–46] as well as computational studies [47, 48]. The catalytically active species is believed to be a metal imido complex, which undergoes a reversible, rate-determining [2 + 2]-cycloaddition with an alkyne, respective allene, to yield an azametallacyclobutene species. Subsequent protonolysis leads to the imine hydroamination product. Isolation and characterization of intermediate azacyclobutene species, which are catalytically competent themselves, is a strong support of the mechanism [41, 43, 49–51]. Although no direct experimental [52, 53]



Scheme 4 Imido mechanism for intermolecular hydroamination of alkynes



Scheme 5 Imido mechanism for hydroamination/cyclization of aminoalkenes

or theoretical [54] evidence was obtained, the same mechanism was proposed for the intramolecular hydroamination of aminoalkenes (Scheme 5). The fact that *secondary* amines do not undergo the hydroamination reaction with most group 4 metal catalysts was interpreted in terms of prohibited formation of the imido species, thus being supportive to the imido mechanism.

More recently, neutral zirconium-based catalysts capable of performing reactions with both primary and secondary amines in intra- [55–57] and intermolecular [57, 58] reactions were reported. The imido mechanism is obviously impossible, and an insertion mechanism, similar to the lanthanide-like mechanism shown in Scheme 2 was proposed [55]. The isolation of an insertion intermediate in an intermolecular alkyne hydroamination reaction is compelling evidence in favor of the insertion mechanism [58].

Pronounced kinetic isotope effects were observed in group-4-metal-catalyzed reactions and have been interpreted in terms of either rate-determining metal-imido formation [59] or concerted insertion/protonolysis [60] similar to that shown in Scheme 3. A large isotopic perturbation of stereoselectivity indicates N–H bond breakage during C–N bond formation [60] and strongly supports the second argument. However, it is not yet clear whether such phenomena are common for all group 4 metal catalysts.

It should be noted that cationic titanium and zirconium catalysts, which are isoelectronic to neutral group 3 metal complexes, cyclize only aminoalkenes with a secondary amino group, whereas primary amines are unreactive [61, 62]. It has been proposed that the lanthanide-like insertion mechanism is operating in these systems, which is in agreement with DFT calculations [63].

3 Intramolecular Hydroamination

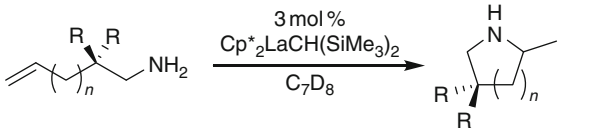
3.1 Hydroamination/Cyclization of Aminoalkenes

Intramolecular hydroamination of aminoalkenes is by far the most intensively explored subfield of hydroamination, which is apparently determined by a relative accessibility of this transformation compared to the intermolecular reaction. Significant progress in catalyst design has been made during the last two decades, in particular rare earth and group 4 metals saw most development while group 1 and 2 catalysts started to emerge more recently. Due to the large amount of material, the catalysts will be discussed separately based on the metal employed.

3.1.1 Lanthanides and Actinides

Among numerous catalytic applications of organolanthanides [64], hydroamination is arguably the most extensively studied transformation. Rare earth metal complexes have proven to be very efficient catalysts for *intramolecular* hydroamination reactions involving aminoalkenes [5, 18]. They are significantly less efficient in *intermolecular* hydroamination reactions and only a limited number of examples are known [20, 65–68]. The difficulties in intermolecular hydroamination reactions originate primarily from inefficient competition between strongly binding amines and weakly binding alkenes for vacant coordination sites at the catalytically active metal center.

Initial studies on the intramolecular hydroamination of aminoalkenes were focused on lanthanocene-based catalyst systems that proved to be efficient in the *exo*-specific cyclization of terminal aminoalkenes to form 5-, 6-, and 7-membered azacycles (Scheme 6) [17]. The reactions are predictably faster for the formation of smaller five-membered rings and in the presence of *gem*-dialkyl substituents [69]. An increasing metal ionic radius and a more open coordination sphere, e.g., in *ansa*-lanthanocenes, are also beneficial for higher cyclization rates [17]. A further increase in catalytic activity was observed when sterically more open and more electrophilic constrained-geometry catalysts (CGC) **1** (Fig. 2) were applied [70]. Notably, sterically open *ansa*-lanthanocenes and constrained-geometry catalysts [27, 31, 72] and more recently also sterically readily accessible non-metallocene catalysts [67, 73, 74] have displayed significant product inhibition (leading to apparent first order kinetics) or



n	R	T/°C	TOF/h^{-1}
1	H	60	140
1	Me	25	95
2	H	60	5
3	Me	60	0.3

Scheme 6 Lanthanocene-catalyzed intramolecular hydroamination of terminal aminoalkenes [17]

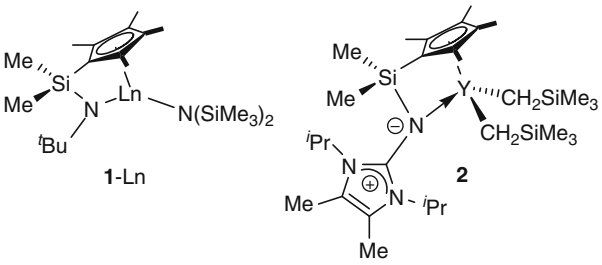


Fig. 2 Constrained geometry rare earth metal hydroamination catalysts [70, 71]

substrate inhibition (resulting in self-acceleration) due to amine coordination to the rare earth metal center.

Although lanthanocene catalysts initially developed for aminoalkene hydroamination are air and moisture sensitive and not readily commercially available, their catalytic activity remains unsurpassed as of now and only a few post-metallocene rare earth metal complexes can reach comparable levels of catalytic efficiency. Besides constrained geometry (Fig. 2) [70, 71] and other half-sandwich [66, 75, 76] rare earth metal complexes, a large number of cyclopentadienyl-free catalyst systems have been developed over the last decade, ranging from simple trisamides $Ln\{N(SiMe_3)_2\}_3$ [74, 77, 78] or bisamide $Sm\{N(SiMe_3)_2\}_2$ [79] to more elaborate ligand frameworks, such as chelating diamides [78, 80–82], diamido-amine [74], aminotroponiminato [83], bis(phosphinimino)methanide [84–88], salicylaldiminato [89, 90], β-diketiminato [89, 91], triazacyclononane-amide [92], benzamidinate [92], tridentate triamine [93], amidate [94], and tris(oxazolinyl)borato [95] ligands. Some catalyst systems are depicted in Fig. 3 and catalytic results are compiled in Table 1. Additionally, many chiral catalyst systems for

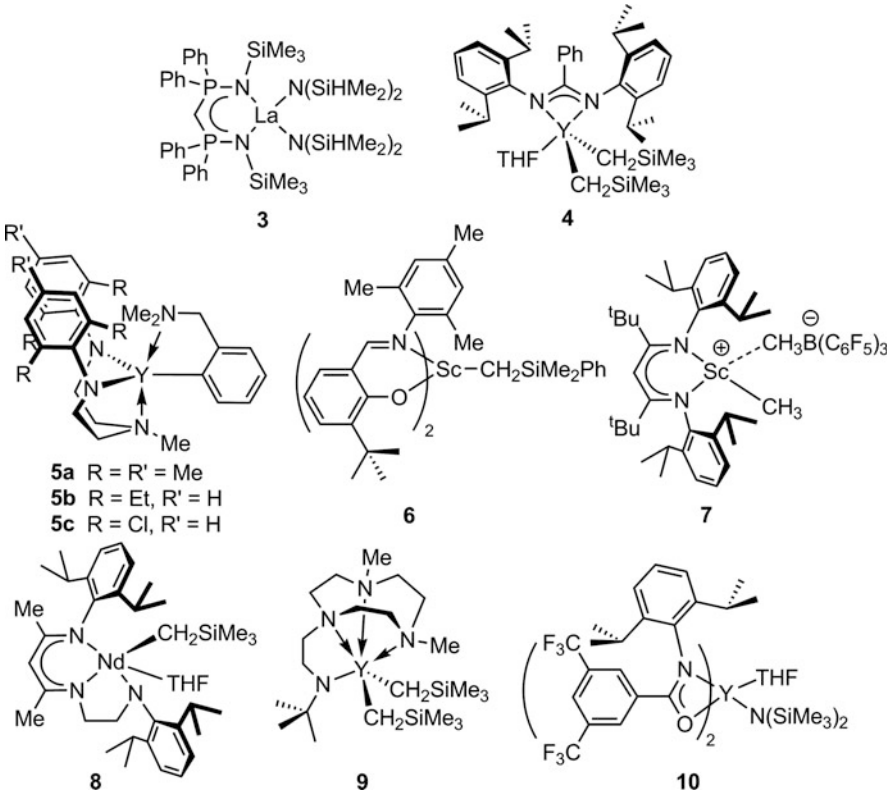
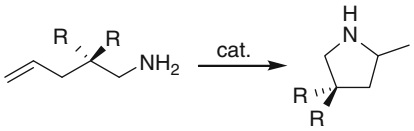


Fig. 3 Selected examples of achiral, non-metallocene rare earth metal-based catalysts for hydroamination of aminoalkenes [74, 89, 91, 92, 94]

Table 1 Hydroamination/cyclization of aminopentenes using post-metallocene rare earth metal catalysts



R	Catalyst	[cat.]/[s], mol%	*T*, °C	*t*, h	Conv., %	Ref.
Me	**1**-Nd	n.r.	25	–[a]	–[a]	[70]
Me	$Y\{N(SiMe_3)_2\}_3$	2.7	24	6	>95	[78]
Me	**3**	1.3	60	6	quant.	[84]
Me	**4**	1	50	0.8	>99	[92]
Me	**5a**	3	25	3.65	95	[74]
Me	**7**	5	65	24	>90	[89]
Me	**8**	0.5	60	1	98	[91]
Me	**9**/$[PhNMe_2H][B(C_6F_5)_4]$	1	50	12	>99	[92]
Me	**10**	10	25	2.5	93	[94]
Ph	**2**	4	r.t.	0.05	quant.	[71]
Ph	**6**	10	65	2	>95	[89]
Ph	**7**	5	25	2	>95	[89]
Ph	**10**	10	25	<0.25	93	[94]

[a]TOF = 200 h^{-1}. n.r. = not reported

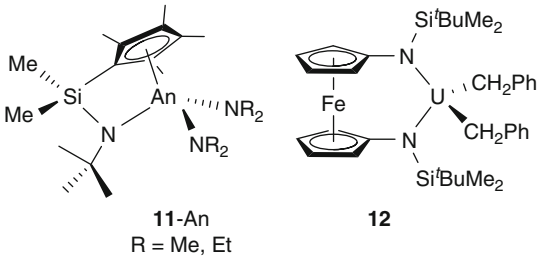
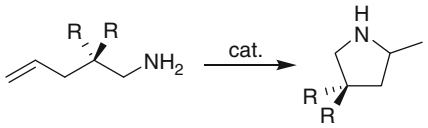


Fig. 4 Actinide catalysts for the hydroamination of aminoalkenes [96–98]

asymmetric hydroamination reactions have been developed (see Sect. 6) in order to overcome significant drawbacks of chiral cyclopentadienyl-containing rare earth metal complexes.

Only a limited number of organoactinide catalysts have been investigated for the hydroamination/cyclization of aminoalkenes (Fig. 4, Table 2) [55, 96–98]. The constrained geometry catalysts **11**-An (An = Th, U) show high activity comparable to the corresponding rare earth metal complexes and can be applied for a broad range of substrates [55, 96, 97]. The ferrocene–diamido uranium complex **12** was also catalytically active for aminoalkene cyclization, but at a somewhat reduced rate [98]. Mechanistic studies suggest that the actinide-catalyzed reaction occurs via a lanthanide-like metal-amido insertion mechanism and not via an imido mechanism (as proposed for alkyne hydroaminations), because also secondary aminoalkenes can be cyclized [55, 98].

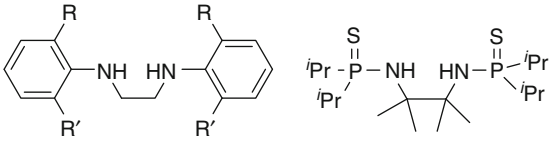
Table 2 Actinide-catalyzed hydroamination/cyclization of aminoalkenes



R	Catalyst	*T*, °C	TOF, h^{-1}	Ref.
Me	**11**-Th	25	15	[96, 97]
Me	**11**-U	25	2.5	[96, 97]
Ph	**11**-Th	25	1460	[96, 97]
Ph	**11**-U	25	430	[96, 97]
Ph	**12**	70	96[a]	[98]

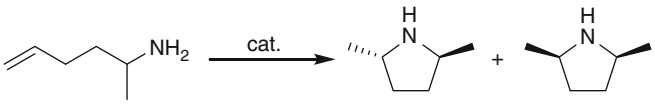
[a]2.5 mol% cat, 88% conv., 22 min

Fig. 5 Chelating diamines used as ligands for non-metallocene hydroamination catalysts



13a R = ^{i}Pr, R′ = H
13b R = R′ = Et

13c

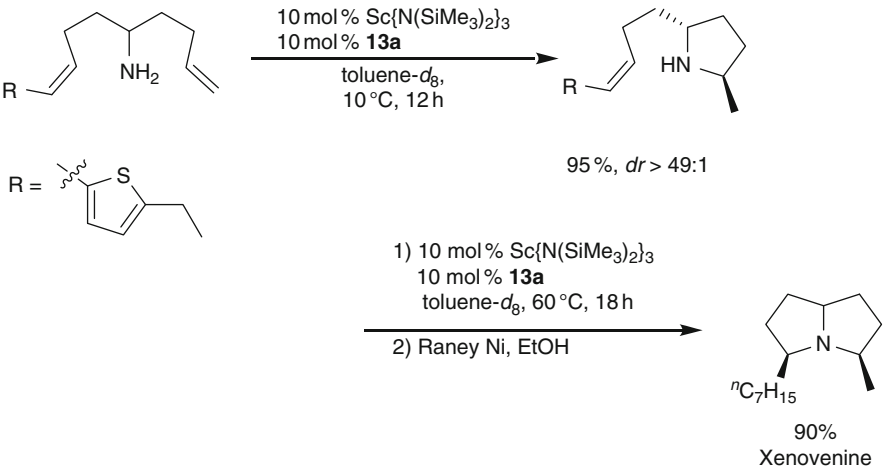


14 *trans*-**15** *cis*-**15**

cat.	conditions	*trans:cis*	yield, %
5 mol % $Sc\{N(SiMe_3)_2\}_3$ + 5 mol % **13a**	60 °C, 1.5 h	49:1	>95
3 mol % **5b**	25 °C, 8 h	23:1	89
$La\{N(SiMe_3)_2\}_3$	90 °C, 13 h	4:1	>99

Scheme 7 Diastereoselective cyclization of **14** [74, 82]

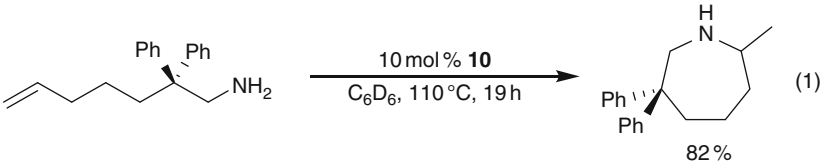
Catalyst systems obtained in situ from rare earth metal trisamides $Ln\{N(SiMe_3)_2\}_3$ and various chelating diamines (e.g., **13a–c**, Fig. 5) have shown good activity in the cyclization of aminoalkenes (Schemes 7 and 9) [78, 80–82]. The more challenging cyclization of the chiral aminoalkene **14** can be accomplished with high *trans*-diastereoselectivity (up to 49:1) at 60°C [82]. The preferred formation of *trans*-**15** can be explained with minimal 1,3-diaxial interactions in the chair-like cyclization transition state [17, 99]. Unfortunately, the structure of most of the chelating diamide catalyst systems is not known. Structurally characterized diamidoamine complexes **5a–c** have shown higher reactivity that allows the reaction to proceed at 25°C with up to 23:1 *trans*-selectivity [74].



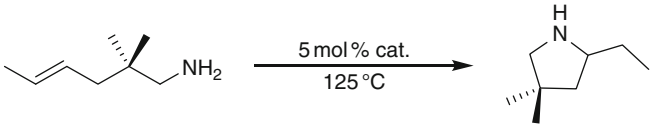
Scheme 8 Preparation of (±)-xenovenine via diastereoselective bicyclization of an amino-bisalkene [100]

The highly diastereoselective hydroamination catalyzed by **13a**/Sc{N(SiMe$_3$)$_2$}$_3$ was applied as a key step in a preparation of (±)-xenovenine (Scheme 8) [100]. Xenovenine is also accessible via a bicyclization of an aminoallene–alkene substrate in both racemic and enantiopure form [101]. Both approaches involve hydroamination with a *secondary* amine, a reaction that often requires a sterically more open rare earth metal catalyst [17].

The formation of seven-membered rings constitutes another significant challenge for post-metallocene catalysts, but can be accomplished utilizing the bis(amidate) yttrium catalyst **10** (1) [94].



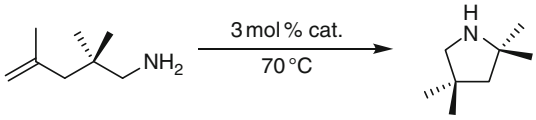
While most rare earth metal-based catalyst systems are neutral, only a few cationic catalyst systems have been investigated. For example, the β-diketiminato scandium complex **7** [89] and the triazacyclononane-amide complex **9** (after treatment with [PhNMe$_2$H][B(C$_6$F$_5$)$_4$]) [92] display improved catalytic activity over their neutral congener. However, this trend is not general, as the opposite result, higher activity for the neutral over the cationic species, was found for the benzamidinate complex **4** [92], Quite generally, it is expected that the metal-amide bond is stronger for the more electron deficient species, thus impeding the insertion process of the olefin into the metal-amide bond. However, the reduced steric strain around the cationic metal center in case of **7** and **9** (after activation with [PhNMe$_2$H][B(C$_6$F$_5$)$_4$])



cat.	*t*, h	TOF, h^{-1}
1-Sm	~5.5	3.59
16-Sm	~1	21.6
$Nd\{N(SiMe_3)_2\}_3$/**13b**	6.5	

Scheme 9 Catalytic hydroamination/cyclization of an aminoalkene with an internal double bond [27, 80]

Scheme 10 Cyclization of a 1,1-disubstituted aminopentene [78, 102]



cat.	*t*, h	yield, %
$[Cp^{TMS}{}_2SmMe]_2$	2	93
$Y\{N(SiMe_3)_2\}_3$	8	94

could compensate for this impediment and result in an overall net rate increase in comparison to the neutral, sterically more congested analogs.

Cyclization of 1,2- and 1,1-disubstituted alkenes requires elevated temperatures and sterically more open and more reactive catalysts [27, 78, 80, 81, 94, 99, 102, 103], such as constrained geometry catalysts $Me_2Si(C_5Me_4)(t\text{-BuN})LnN(SiMe_3)_2$ (**1**), *ansa*-lanthanocenes $Me_2Si(C_5Me_4)_2LnCH(SiMe_3)_2$ (**16**), or non-metallocene complexes with chelating bis(amides) (Schemes 9 and 10), while trisubstituted alkenes remain challenging.

Compared to homogeneous catalysts, heterogeneous catalysts have the significant advantage that the catalyst may be easily removed from the reaction mixture and can potentially be recycled. Lanthanocene complexes may be attached to amine-functionalized cross-linked polystyrene supports (2) [104]. The supported catalysts, e.g., **18**, displayed activities similar to their homogeneous analogs and could be recycled at least two times with moderate loss of activity (Table 3). The immobilized form of the catalyst is released from the support via transamination by the aminoalkene substrate and the catalytic cycle proceeds then homogeneously in solution. After all the substrate has been consumed, the catalyst can return to the polymer support in order to allow catalyst separation and recycle.

Interestingly, homoleptic trisamides grafted on partially dehydroxylated mesoporous zeolites exhibited activities higher than that of the trisamides in homogeneous solution. The activity decreases in the row Y > La > Nd and is also dependent on the pore size and particle morphology [105].

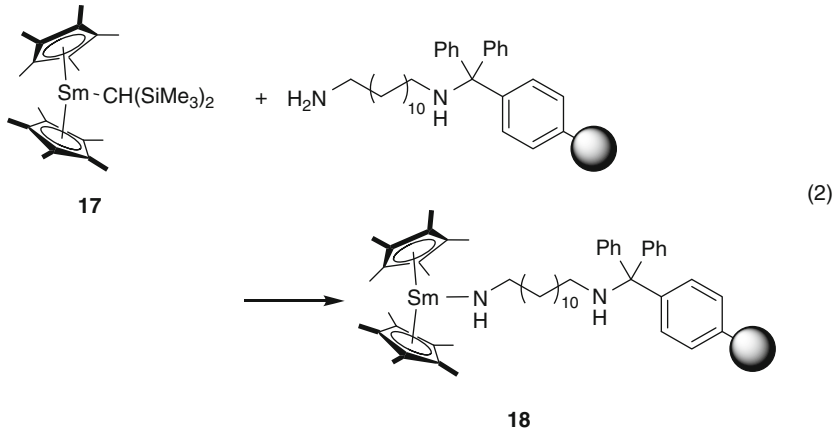
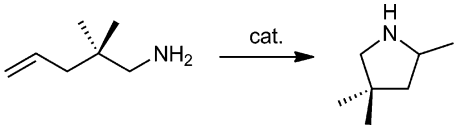


Table 3 Hydroamination/cyclization of dimethylaminopentene catalyzed by homogeneous and supported rare earth metal catalysts



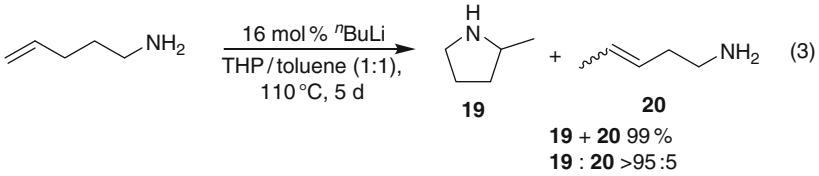
Catalyst	[cat.]/[s], mol%	Cycle	T, °C	TOF[a]	t, h	Ref.
17	5	1	60	30	0.6[b]	[104]
18	5	1	60	20	0.9[b]	[104]
18	5	2	60	11	1.6[b]	[104]
18	5	3	60	7	2.5[b]	[104]
$Y\{N(SiMe_3)_2\}_3$	3	1	50	16	1.9	[105]
$Y\{N(SiMe_3)_2\}_3$@SBA-15LP	3	1	50	36	0.9	[105]
$Y\{N(SiMe_3)_2\}_3$@SBA-15LP	6	1	70	>200	0.05	[105]
$Y\{N(SiMe_3)_2\}_3$@SBA-15LP	6	2	70	49	0.33	[105]
$Y\{N(SiMe_3)_2\}_3$@SBA-15LP	6	3	70	1	15	[105]

[a]Average turnover frequency, h^{-1}
[b]Time required for 90% conv

3.1.2 Main Group Metal Catalysts

Although organolanthanide catalysts possess unsurpassed reactivity in intramolecular hydroamination, the development of more robust, environmentally benign, and readily available catalysts remains an important target. Main group metal complexes resemble organolanthanides in key parameters such as high electrophilicity and the ability to mediate C=C insertion as well as σ-bond metathesis. Thus, it is not too surprising that main group metal derivatives also catalyze hydroamination/cyclization of aminoalkenes.

Organolithium compounds would be extremely desirable catalysts since the organometallic precursors such as alkyllithiums are readily available. It was found that intramolecular hydroamination of aminoalkenes can be mediated by a catalytic amount of *n*-butyllithium [35, 106]. The obvious drawback is the high basicity of lithium amides, which can result in double bond isomerization side reactions. Optimal conditions were found using a solvent mixture of THP and toluene at 110°C (3) although the reaction also proceeds at lower temperatures.



Despite some success in the design of stereoselective organolithium-based catalysts which are more active and less prone to side-reactions (see Sect. 6.1.2), it is not yet clear whether a general and efficient alkali metal catalyst can be designed in principle, considering the fundamental limitations of these compounds.

Alkaline earth metal complexes are typically less basic than organolithiums and they are therefore promising candidates for the development of efficient catalysts. Recently, several catalytic systems have been introduced (Fig. 6). A summary of the catalytic results is presented in Table 4.

Calcium and magnesium β-diketiminates were shown to catalyze hydroamination/cyclization of terminal primary and secondary aminoalkenes with reasonable reactivity (Table 4, entries 1–5) [36, 39, 107]. While the reactivity of calcium species

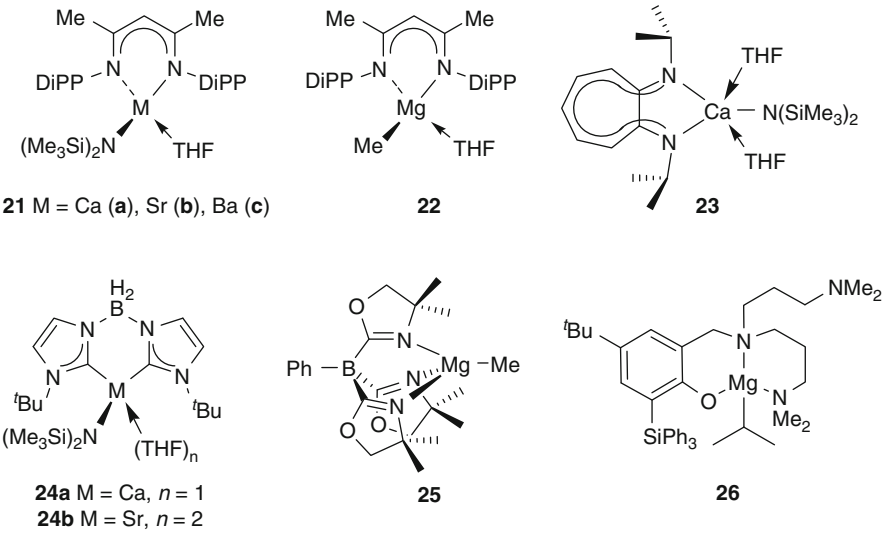
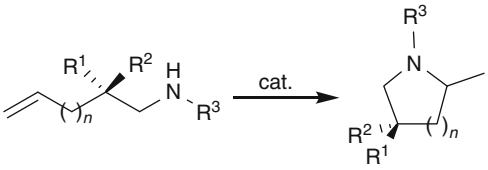


Fig. 6 Selected alkaline earth-metal-based catalysts (DiPP = 2,6-diisopropylphenyl) [36, 38, 39, 107–111]

Table 4 Alkaline earth-metal-catalyzed hydroamination/cyclization of aminoalkenes



Entry	*n*	R^1, R^2	R^3	Cat.	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	Ref.
1	1	H, H	H	**21a**	10	25	21	90	[36]
2	1	Ph, Ph	H	**21a**	2	25	0.25	99	[36]
3	1	Ph, Ph	H	**22**	2	25	2	99	[36]
4	1	H, H	allyl	**21a**	10	25	48	60	[36]
5	3	Ph, Ph	H	**22**	5	80	132	88	[36]
6	1	H, H	H	**23**	10	25	40	>90	[108, 109]
7	1	Ph, Ph	H	**24a**	5	25	0.3	95	[110]
8	1	Ph, Ph	H	**24b**	5	25	0.15	>99	[110]
9	2	Ph, Ph	H	**24a**	5	25	24	60	[110]
10	2	Ph, Ph	H	**24b**	5	25	4	88	[110]
11	1	Ph, Ph	H	**25**	10	50	12	99	[38]
12	1	Ph, Ph	H	**26**	3	25	3	99	[111]

21a was superior to that of its magnesium analog **22**, only **22** could serve as a catalyst for more challenging substrates such as aminoheptene (Table 4, entry 5) since **21a** was undergoing fast ligand redistribution accompanied with catalyst deactivation at elevated temperatures [36]. The aminotroponiminato calcium complex **23** showed activity comparable to **21a** for the formation of pyrrolidines (Table 4, entry 6) [108, 109]. The influence of the size of the ionic radius is less straightforward for alkaline earth metal catalysts compared to the lanthanides. The highest activity is commonly observed for the calcium catalysts with magnesium and strontium being less active [36, 39, 109, 112]. However, the bis(imidazolin-2-ylideneyl)borate complexes **24** seem to be an exception, as the strontium complex **24b** was found to be superior to its calcium analog **24a** [110] (Table 4, entries 7–10).

In general, the feasibility of Schlenk-type equilibria for most alkaline earth metal species poses a remarkable challenge to design well-defined species that are stable under catalytically relevant conditions. The unwanted ligand redistribution is more facile for larger alkaline earth metal ions, thus magnesium complexes are probably the most promising candidates to obtain stable catalysts. In addition, stereoelectronic factors of the ligand framework may implement the feasibility of unwanted side reactions. Thus, ligand redistribution was reported to be suppressed for the chelating polydentate oxazolinborate **25** [38] and aminophenolate **26** [111], although both displayed reactivity lower than that of **22** (Table 4, entries 11 and 12 vs. entry 3). The Schlenk equilibrium may also be suppressed by utilizing a bidentate imine-amido ligand [113].

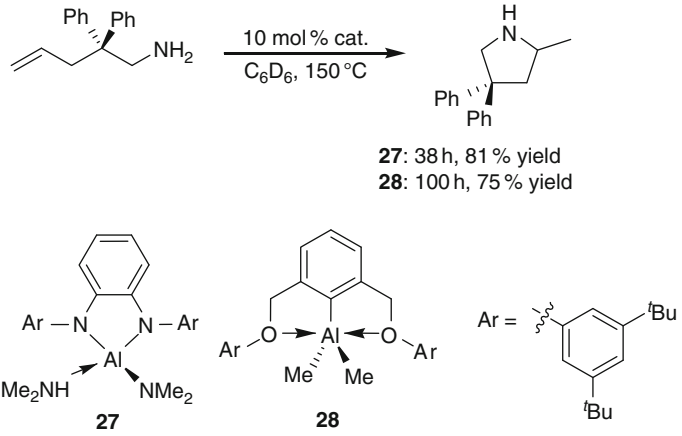


Fig. 7 Aluminum-catalyzed intramolecular hydroamination

The importance of suppressing the ligand redistribution is also of relevance for asymmetric hydroamination reactions catalyzed by chiral alkaline earth metal catalysts (see Sect. 6.1.3).

Several examples of organoaluminum-catalyzed hydroamination of aminoalkenes have been reported recently. The neutral amido bis(anilide) **27** [37] and the aluminum pincer diolate complex **28** [114] displayed low catalytic activity and were only applicable to *gem*-disubstituted aminopentenes (Fig. 7).

These examples illustrate that main group metal-based catalysts have the potential to be viable alternatives to rare earth metal catalysts. However, significant research efforts are necessary to improve these systems further.

3.1.3 Group 4 Metal Catalysts

The application of group 4 metal complexes to intramolecular alkene hydroamination has become a vibrant and quickly developing field since the first reports appeared around 2004 [52, 53, 61, 62]. Several important features of these catalysts strikingly differentiate those systems from rare earth or alkaline earth metal catalysts. First, despite some significant improvements, the reactivity of group 4 metal catalysts (Fig. 8) remains low compared to rare earth metals, thus demanding higher catalyst loadings and temperatures (Table 5). Most catalysts are restricted to *gem*-dialkyl-activated substrates and terminal alkene moieties. Harsh reaction conditions often result in side reactions, namely double bond isomerization and hydroaminoalkylation [120]. In addition, only a few systems are capable of cyclizing both primary and secondary aminoalkenes as opposed to rare earth metals (see Sect. 2.2).

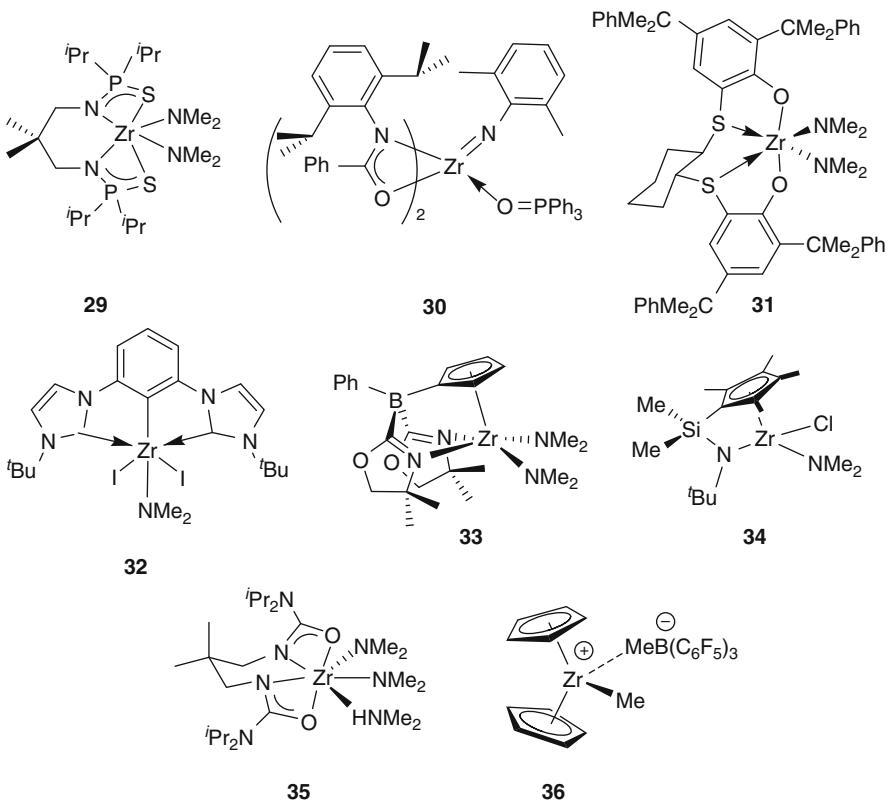
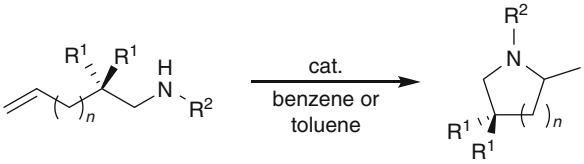


Fig. 8 Selected group-4-metal-based catalysts for hydroamination/cyclization of aminoalkenes [52, 55, 57, 61, 115–118]

Simple homoleptic amides of titanium [53] and zirconium [56] can be used as catalysts for the cyclization of activated aminopentenes (Table 5, entries 1 and 2). Nonactivated substrates and larger rings are not accessible, and only sterically shielded and more reactive catalysts are capable of cyclizing the more challenging substrates. It should be noted that zirconium catalysts are significantly more reactive than their titanium analogs in hydroamination of aminoalkenes in contrast to the reactivity scale found for the hydroamination of alkynes (Sect. 5.4). The bis(thiophosphinic amidate) **29** was active in the cyclization of the aminopentene lacking *gem*-dialkyl-substituents (Table 5, entry 5), although a reaction temperature of 150°C was required [52]. The zirconium amidate **30** [115], the [OSSO]-type bis-(phenolate) **31** [116], and the NHC-supported pincer complex **32** [117] exhibited lower reactivity than $Zr(NMe_2)_4$ (Table 5, entries 2 and 6–8) and were not applicable to substrates without *gem*-dialkyl-substituents. Similarly, the bis(indenyl)

Table 5 Group-4-metal-catalyzed hydroamination/cyclization of aminoalkenes



Entry	*n*	R^1	R^2	Catalyst	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	Ref.
1	1	Ph	H	$Ti(NMe_2)_4$	5	110	24	92	[53]
2	1	Ph	H	$Zr(NMe_2)_4$	5	100	1	92	[56]
3	1	Ph	H	Ind_2TiMe_2	5	105	24	96	[119]
4	1	Me	H	Ind_2TiMe_2	5	105	24	74	[119]
5	1	H	H	**29**	10	150	10	91	[52]
6	1	Ph	H	**30**	5	110	4	98	[115]
7	1	Ph	H	**31**	5	105	24	82	[116]
8	1	Ph	H	**32**	5	160	0.83	98	[117]
9	1	Me	H	**33**	10	23	11	85	[118]
10	1	H	H	**33**	10	23	33	62	[118]
11	1	Ph	Me	**34**	n.r.	90	–[a]	95	[55]
12	1	Ph	Me	**35**	10	100	4	90	[57]
13	3	Ph	H	**35**	10	145	20	90	[57]
14	1	H	Me	**36**	2	80	7	98[b]	[61]

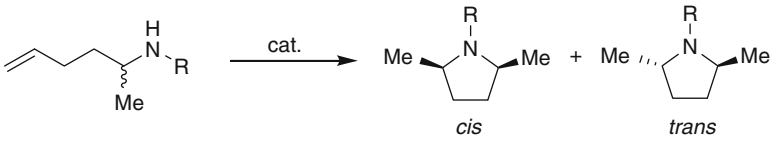
[a]TOF 0.4 h^{-1}
[b]Reaction in C_6D_5Br. n.r. = not reported

complexes Ind_2MMe_2 (M = Ti, Zr, Hf) were less active than $Ti(NMe_2)_4$ and the activity generally decreased in the order Ti > Zr > Hf [119].

A dramatic increase in reactivity was observed for the zwitterionic zirconium cyclopentadienyl-bis(oxazolidinyl)borate complex **33** [118]. The hydroamination reactions proceeded readily at room temperature, thus significantly exceeding the reactivity of most zirconium analogs. Despite the high reactivity, cyclization of the unsubstituted aminopentene did not proceed to high conversion even at high catalyst loading (Table 5, entry 10) possibly due to an autoinhibition [118].

It is noteworthy that neutral group 4 metal hydroamination catalysts are limited to primary aminoalkenes, while they are generally unreactive toward *secondary* aminoalkenes. Only a few catalyst systems, for example, the constrained geometry complex **34** [55] and the bis(ureate) **35** [57], among others [56, 119], are capable of cyclizing both primary and secondary aminoalkenes, which apparently marks the mechanistic difference displayed by these catalysts (Sect. 2.2). **35** is one of the few zirconium catalysts allowing facile chemoselective seven-membered ring closure (Table 5, entry 13). The cationic zirconocene **36**, which is isoelectronic to lanthanocenes, showed good activity in the hydroamination/

Table 6 Group-4-metal-catalyzed diastereoselective hydroamination/cyclization of chiral aminopentenes



R	Cat.	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	*cis*:*trans*	Ref.
H	**29**	5	150	22	96	1:1.3	[52]
H	**30**	10	110	96	72	1:11	[115]
Me	**36**	2	80	15	97	3:1	[61]

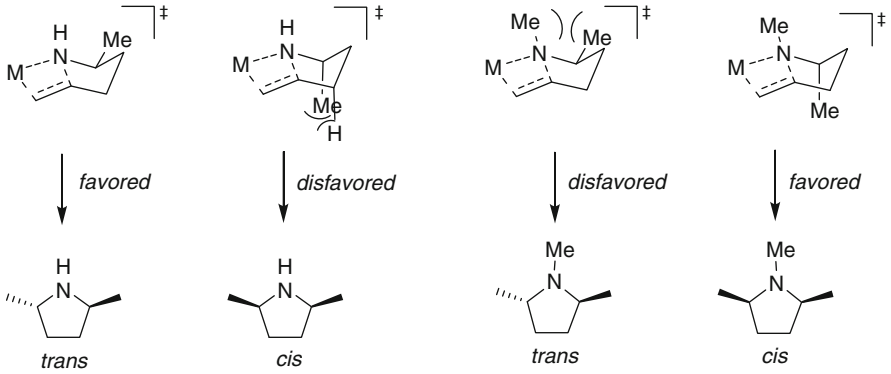
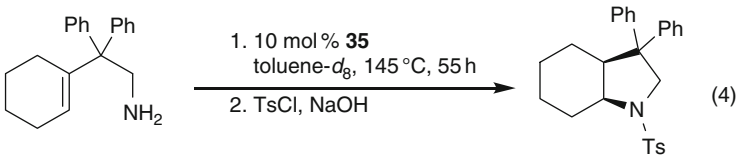


Fig. 9 Stereomodels for observed diastereoselectivity in the cyclization of α-substituted aminopentenes (shown for insertion mechanism)

cyclization of *secondary* aminoalkenes (Table 5, entry 14), but was unreactive toward primary aminoalkenes [61].

Diastereoselective cyclizations of chiral aminoalkenes were also achieved for zirconium catalysts (Table 6). Interestingly, the cyclization of primary aminoalkenes gave predominately *trans*-disubstituted pyrrolidines in accordance to observations for rare earth metal-based hydroamination catalysts [17, 67, 74, 80–82, 99, 121, 122], while the *cis*–diastereomer was favored in case of the secondary aminoalkene. Plausible transition states are shown in Fig. 9. The chair-like transition state leading to the *trans*-isomer of the primary aminoalkene is less encumbered due to reduced 1,3-diaxial interactions, whereas *gauche* interactions of the *N*-substituent make the *cis*-pyrrolidine the preferred product in case of secondary aminoalkenes.

Internal and even trisubstituted double bonds can also be involved in group-4-metal-catalyzed hydroamination/cyclization; however, harsher reaction conditions are typically required (4) [57].



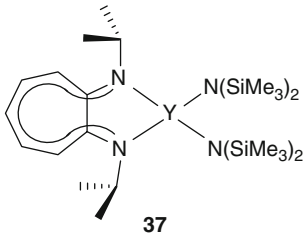
3.2 *Hydroamination of Aminoalkynes*

3.2.1 Rare Earth Metal Catalysts

The rare earth metal-catalyzed hydroamination/cyclization of internal and terminal aminoalkynes is a facile process, as shown by experimental [28, 29] and theoretical [32] studies. In general, the reaction proceeds via the same mechanism as aminoalkene hydroamination (Scheme 2) with some notable difference arising from a different insertive reactivity of the triple bond. The insertion of the C–C triple bond proceeds much faster than that of a double bond due to the exothermic nature of the insertion step (Fig. 1). Overall, the cyclization of an aminoalkyne is commonly 1–2 orders of magnitude faster than that of an analogous terminal aminoalkene. However, the insertion step is still considered to be the rate-determining step, based on aforementioned DFT calculations and experimental observations.

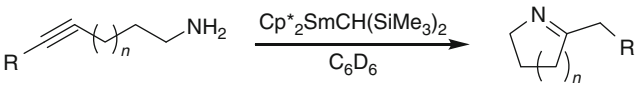
Interestingly, the reactivity pattern in rare earth metal-catalyzed hydroamination/cyclization reactions of aminoalkynes with respect to ionic radius size and steric demand of the ancillary ligand follows the opposite trend to that observed for aminoalkenes, namely *decreasing* rates of cyclization with *increasing* ionic radius of the rare earth metal and more open coordination sphere around the metal. This phenomenon can be explained by a negligible sterical sensitivity of a sterically less encumbered triple bond, as sterically less open complexes and smaller metal ions provide more efficient reagent approach distances and charge buildup patterns in the transition state [32].

Selected examples of intramolecular aminoalkyne hydroamination are shown in Scheme 11, Table 7, and Fig. 10. Formation of 5-, 6-, and 7-membered cyclic imines has been achieved in excellent yields.



37

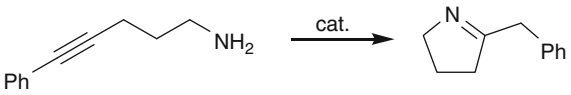
Fig. 10 An aminotroponiminato catalyst for hydroamination of aminoalkynes [83]



n	R	*T*, °C	TOF, $/h^{-1}$
1	H	21	580
1	Me	21	96
1	$SiMe_3$	21	>7600
1	Ph	60	2830
2	Ph	60	328
3	Ph	60	0.11

Scheme 11 Samarocene-catalyzed hydroamination/cyclization of aminoalkynes [28, 29]

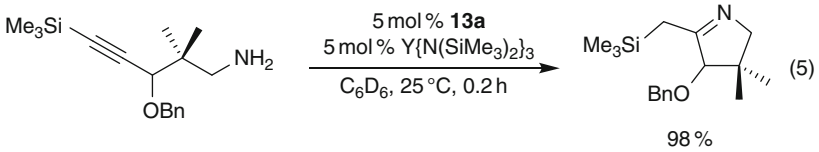
Table 7 Rare earth metal-catalyzed hydroamination/cyclization of aminoalkynes



Catalyst	[cat.]/[s], mol%	*T*, °C	*t*, h	Conv., %	Ref.
3[a]	1	60	1	quant.	[84]
5c[a]	3	60	0.25	93	[74]
6[a]	10	25	0.75	>95	[89]
7[a]	10	25	0.75	>90	[89]
$Y\{N(SiMe_3)_2\}_3$/**13c**	5	60	1.5	96	[123]
37	2	21	100	quant.	[83]

[a]See Fig. 3

Catalyst systems derived from $Ln\{N(SiMe_3)_2\}_3$ and chelating diamines (e.g., **13a**, Fig. 5) are also active in the cyclization of aminoalkynes with quite remarkable activity and functional group tolerance (5) [123].

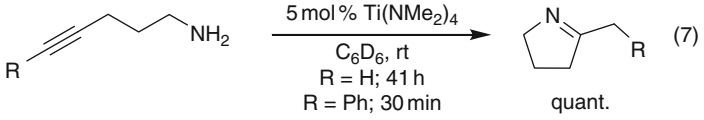


The rare earth metal-catalyzed cyclization of aminoalkenes, aminoalkynes, and aminodienes generally produces exclusively the exocyclic hydroamination products. The only exception was found in the cyclization of homopropargylamines leading to the formation of the endocyclic enamine product via a 5-*endo-dig* hydroamination/cyclization (6) [124], most likely due to steric strain in a potential four-membered ring exocyclic hydroamination product. Interestingly, the 5-*endo-dig* cyclization is still preferred even in the presence of an alkene group that would lead to a 6-*exo* hydroamination product [124].

(6)

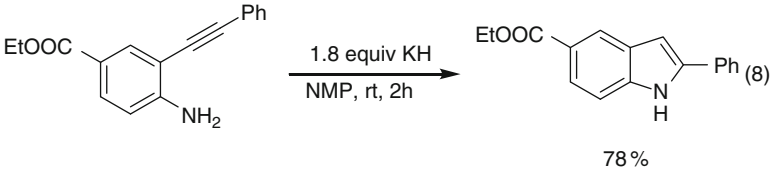
3.2.2 Other Metals

As discussed in Sect. 5, the intermolecular hydroamination of alkynes catalyzed by group 4 metal complexes is a well-documented process. The less challenging intramolecular transformation can be achieved efficiently with various titanium-based catalysts [51, 125–130]. The cyclization proceeds analogously to the rare earth metal-catalyzed process with exclusive *exo*-selectivity and often requires elevated temperatures. However, the homoleptic titanium tetraamide $Ti(NMe_2)_4$ catalyzes the cyclization of both terminal and internal aminoalkynes at room temperature (7) [126, 127].



(7)

Catalysts based on metals other than rare-earth or group 4 elements are significantly less explored. Several interesting examples employing robust basic alkali metal derivatives as mediators of alkyne hydroamination were disclosed [131, 132]. The cyclization of 2-alkynyl anilines proceeded smoothly in the presence of KH or CsOH, although often stoichiometric amount of base was employed. Notably, many functional groups sensitive to organometallic catalysts are tolerated (8) [132]. However, the method is apparently restricted to more acidic amine derivatives, such as anilines.



(8)

3.3 *Hydroamination of Conjugated Aminodienes*

Organolanthanide-catalyzed hydroamination of conjugated dienes is a facile process due to the transient formation of an η^3-allyl intermediate, which forms *E*/*Z*-vinylpyrrolidines and vinylpiperidines upon protonation, and, under certain conditions, also allyl isomers (Fig. 11, Scheme 12). Cyclizations with lanthanocenes

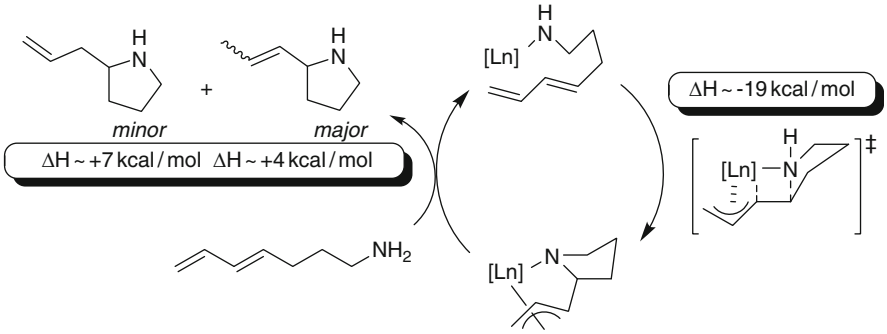
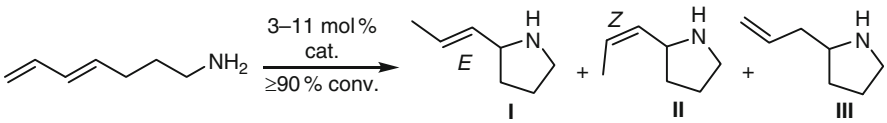


Fig. 11 Mechanism of rare earth metal-catalyzed aminodiene cyclization [30, 31]



cat.	T / °C	I : II : III	TOF / h^{-1}
$Cp^*_2LaCH(SiMe_3)_2$	25	84 : 16 : 0	40
$Cp^*_2YCH(SiMe_3)_2$	60	30 : 19 : 51	0.05
1-Sm	25	59 : 41 : 0	3.1
1-Y	25	87 : 13 : 0	~0.08

Scheme 12 Cyclization of aminoheptadiene [30, 31]

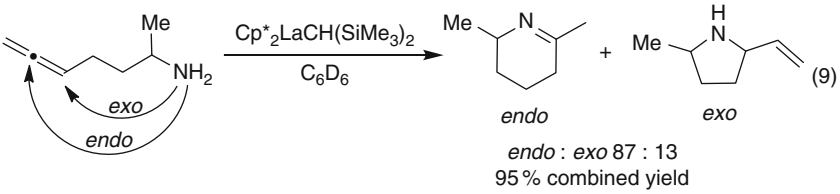
lead preferentially to the *E* alkene in up to 98:2 *E*/*Z* ratio [30, 31]. The allylpyrrolidine becomes the prevailing product at a dramatically reduced reaction rate for the sterically more congested $Cp^*_2YCH(SiMe_3)_2$. Generally, the reaction rates are higher for aminodienes compared to the corresponding aminoalkenes, despite increased steric encumbrance of the cyclization transition state. DFT calculations indicate that the high stereo- and regioselectivities result apparently from kinetically impeded protonolysis of the more substituted atom of the stabilized allyl intermediate (Fig. 11) [26, 33, 133]. According to these studies, the protonolysis step might be rate determining due to the facile insertion step. Hydroamination/cyclization of aminodienes shows a rate dependence on the Ln^{3+} ionic radius and coordinative unsaturation that is even more pronounced than in the case of aminoalkenes [31].

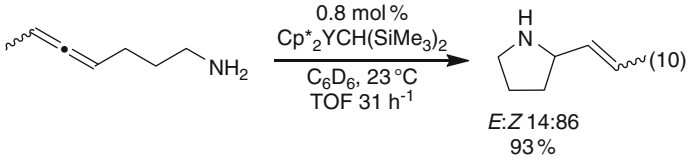
Early transition metals or main group metals other than the rare earth elements have been scarcely used in intramolecular diene hydroamination. However, the lithium amide-catalyzed cyclization of aminodienes was recently reported [134, 135] in the context of asymmetric hydroamination and will be discussed in Sect. 6.2.

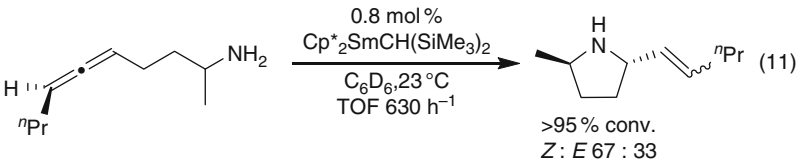
3.4 Hydroamination of Aminoallenes

3.4.1 Rare Earth Metals

The rare earth metal-catalyzed hydroamination of aminoallenes proceeds faster than cyclization of aminoalkenes, but slower than that of aminoalkynes. Two insertion pathways are feasible to yield a mixture of *exo*- and *endo*-products in case of monosubstituted allenes (9) [136, 137]. The cyclization of 1,3-disubstituted allenes on the other hand proceeds exclusively via the *exo* route to generate the vinylic amine (10) and α-substituted aminoallenes cyclize with high diastereoselectivities to give the 2,5-*trans*-pyrrolidines exclusively (11). However, in the latter case the *E*/*Z* ratio is lower in comparison to the high selectivities observed for aminodienes. This potential disadvantage becomes irrelevant if the amine is subjected to subsequent hydrogenation [101], providing an alternative synthetic access to 2-alkyl azacycles instead of a more sluggish cyclization of an aminoalkene with a 1,2-disubstituted double bond [27].





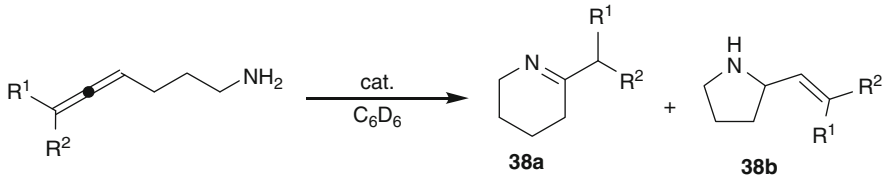


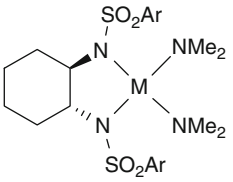
The kinetic analysis demonstrated an unusual dependence of the cyclization rate on the rare earth metal ion size, with maximum turnover rates observed for the medium-sized yttrium and slower rates for the larger lanthanum and smaller lutetium [137]. As for aminoalkynes, catalysts with more open ligand frameworks are less active. DFT calculations indicate that protonolysis is the rate-determining step of the process [25, 34], although this notion is contrary to some experimental observations [136, 137].

3.4.2 Group 4 Metals

Aminoallenes can be readily cyclized using various group 4 metal complexes. Similar to rare earth metal catalysts, control of regio- and stereoselectivity is a central problem. However, strikingly different patterns are observed in the case of titanium and zirconium catalysts (Table 8). The hydroamination of terminal aminoallenes resulted in the regiospecific *endo* cyclization to form the six-membered cyclic imine **38a** using $Ti(NMe_2)_4$ as catalyst (Table 8, entry 1) [126, 127]. The same product, albeit with significantly enhanced productivity, was also obtained exclusively employing the bis-(sulfonamidate) titanium precatalyst **39a** (Table 8, entry 2) [126, 127]. Disubstituted allenes required more forcing conditions, and remarkably, the regioselectivity was inverted in case of the zirconium complex **39b**, yielding vinylpyrrolidine **38b** predominately (Table 8, entry 3 vs. 4). Interestingly, while the regioselectivity remained relatively moderate, the vinylpyrrolidine was obtained with high *Z*/*E* selectivity. Trisubstituted aminoallenes are significantly less reactive (Table 8, entry 5). The zirconium bis(thiophosphinic amidate) **29** (Fig. 8) displayed high regioselectivity for disubstituted allenes, yielding the vinylpyrrolidine specifically (Table 8, entry 6)

Table 8 Group-4-metal-catalyzed hydroamination of aminoallenes





39a M = Ti, Ar = 4-MeC_6H_4
39b M = Zr, Ar = 2,4,6-$Me_3C_6H_2$

Entry	R^1	R^2	Cat.	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	**38a**:**38b**	**38b**, *Z*/*E*	Ref.
1	H	H	$Ti(NMe_2)_4$	5	75	3	quant.	100:0	–	[126, 127]
2	H	H	**39a**	5	25	5	quant.	100:0	–	[126, 127]
3	Et	H	**39a**	5	75	2	70	100:0	–	[127]
4	Et	H	**39b**	5	75	n.r.[a]	62	25:75	>20:1	[127]
5	Me	Et	**39b**	10	135	n.r.[a]	88	1:11	1.8:1	[127]
6	Me	H	**29**	5	75	2	96	0:100	2:1	[138]
7	H	H	Cp_2ZrMe_2	5	135	18	19	16:3	–	[127]
8	H	H	**36**	5	135	18	quant	34:66	–	[127]

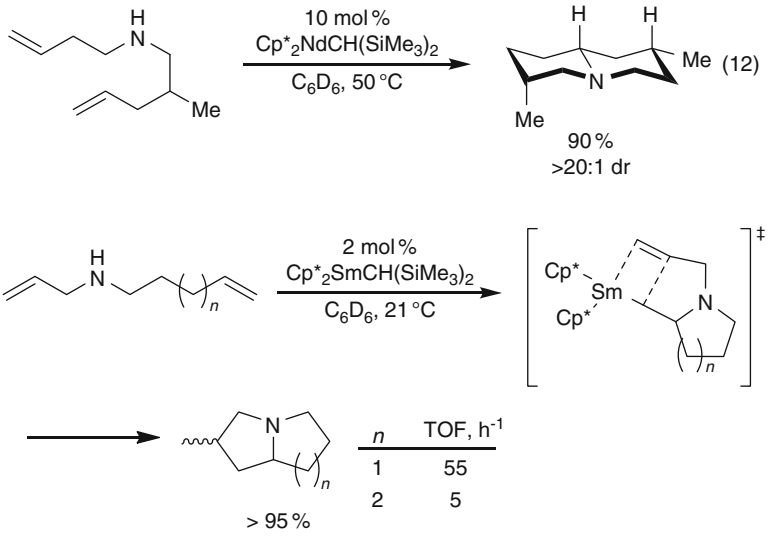
[a]n.r. = not reported

[138]. Interestingly, the amount of vinylpyrrolidine can also be increased by using the *cationic* zirconocene **36** (Fig. 8; Table 8, entries 7–8). Computational studies suggest that neutral [48] and cationic [63] catalyst systems operate via different mechanisms.

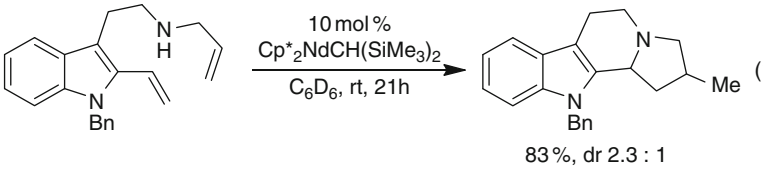
4 Hydroamination/Bicyclization

The hydroamination/bicyclization of dialkenylamines, dialkynylamines and alkenylalkynylamines opens a straightforward route to a family of bicyclic amines in a tandem C–N and C–C bond-forming process. An important prerequisite for the success of this reaction sequence is a sufficient lifetime of the metal alkyl intermediate formed in the initial insertion process of the alkene/alkyne in the metal-amide bond in order to permit the carbocyclization step. Close proximity of the unsaturation to the metal-amide moiety allows facile bicyclization over protonolysis leading to the "normal" hydroamination product. Lanthanocene catalysts have been found applicable for this transformation (Scheme 13) [23, 139].

The scope of this process has been extended in a more detailed investigation to the synthesis of quinolizidines [21] and the influence of alkyl substituents in various positions of the dialkenylamine substrate on product diastereoselectivity was probed. Neodymium-based catalysts are particularly efficient for six-membered ring formation (12). The methodology has found further application in the synthesis of tri- and tetracyclic alkaloidal skeletons (13) [22].

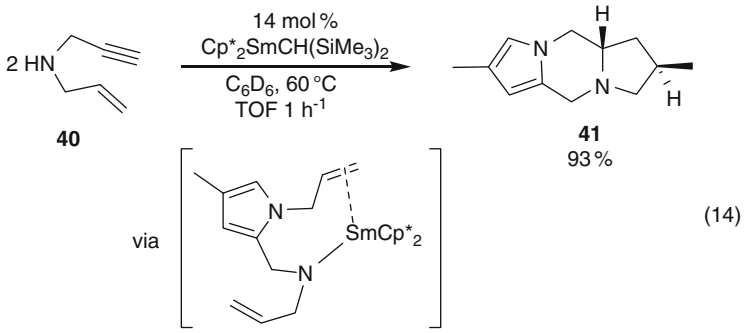


Scheme 13 Synthesis of pyrrolizidines ($n = 1$) and indolizidines ($n = 2$) via hydroamination/bicyclization [23, 139]



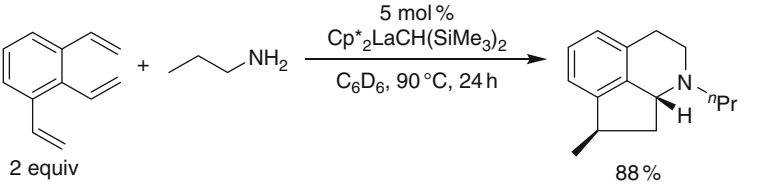
(13)

The carbocyclization step needs to be intramolecular in order to afford the desired product while the hydroamination step may also be intermolecular. Thus, a sequence of *inter*- and *intra*molecular hydroaminations and carbocyclizations of the alkenylalkynylamine **40** substrate allows the facile assembly of the tricyclic polyheterocycle **41** with exclusive *trans* diastereoselectivity (14) [23].



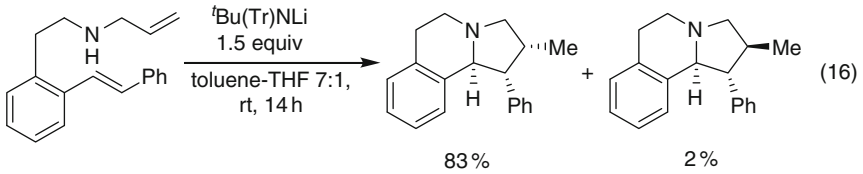
(14)

Trivinylbenzene may be utilized in a hydroamination/carbocyclization process that is initiated by an intermolecular *anti*-Markovnikov addition of *n*-propylamine followed by an intermolecular hydroamination and a highly diastereoselective carbocyclization step (15) [20].



(15)

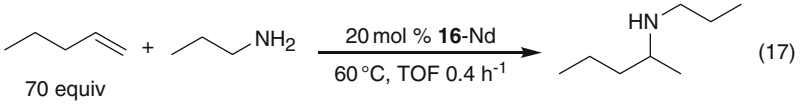
More recently the catalyst scope was extended to organolithium species [24]; however, the reaction is confined to activated (alkenyl)aminostilbenes and yields pyrrolizidine and indolizidine derivatives. A toluene–THF mixture was used as reaction medium and the presence of excess amount of lithium *tert*-butyltritylamide was required to obtain the bicyclization product (16). In the presence of substoichiometric amounts of the lithium-amide, only the hydroamination product was observed.



5 Intermolecular Hydroamination

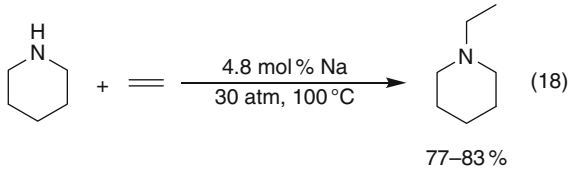
5.1 Hydroamination of Unactivated Alkenes

While the *intra*molecular hydroamination of aminoalkenes is catalyzed efficiently by a variety of catalyst systems, the *inter*molecular hydroamination of alkenes is significantly more challenging. For rare earth metal-based catalysts only a limited number of reports utilizing either lanthanocene [20, 65], phenylene-bridged binuclear half-sandwich [66], or binaphtholate [67, 68] complexes have been documented in the literature. The Markovnikov-addition to an unactivated alkene requires large excess of the alkene in order to overcome the competition between strongly binding amines and weakly binding alkenes, even if the sterically open *ansa*-lanthanocene $Me_2Si(C_5Me_4)_2NdCH(SiMe_3)_2$ (**16**-Nd) is employed (17) [65].



The intermolecular hydroamination of unactivated alkenes with alkali metal catalysts has been known for a long time and a comprehensive review is available [7]. Reactions with ammonia or primary amines catalyzed by elemental lithium [140], sodium [141–144], potassium [141], alkali metal hydrides [141], and amides [145, 146] with ethylene typically require high reaction temperatures (250–500°C) and pressures (up to 1000 bar) and result in mixtures of mono-, di- and triethylamine in moderate yields.

Reactions of secondary amines are more practical (18) [147]. The selective formation of tertiary amines can be achieved by employing alkali metals in their elemental form [144, 147], as alkali metal amides [148–152], which can also be generated in situ from the corresponding metal alkyls, or from metal hydrides [153].

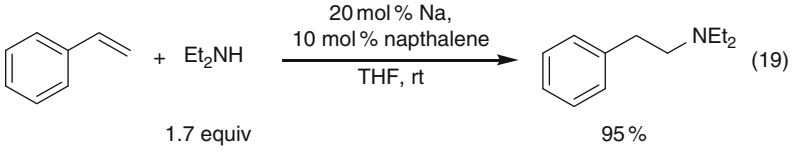


Alkali metal-catalyzed hydroaminations of unactivated higher alkenes is significantly less feasible [148, 152].

The double bond in vinyl arenes is activated as a result of its conjugation to the aromatic ring system. Hence, vinyl arenes generally react more smoothly in hydroamination reactions in comparison to simple, unactivated alkenes, especially in intermolecular processes.

Contrary to simple aliphatic-substituted alkenes, the metal-catalyzed hydroamination of vinyl arenes proceeds usually with high *anti*-Markovnikov selectivity to give β-phenethylamine derivatives (Fig. 12). This reversal of regioselectivity may be explained with the alkene insertion step proceeding through the sterically more encumbered transition state which is favored due to attractive metal–arene interactions and resonance stabilization of the benzyl carbanion. The same selectivity pattern is observed for alkali [40] and alkaline earth [154, 155] metal catalysts and is also explained by metal-aryl interactions as shown by DFT-calculations [40].

Due to the high reactivity of vinyl arenes, a broader range of catalysts is available, including very robust and readily accessible compounds. Sodium metal readily catalyzes the hydroamination of styrene with secondary [156–160] or primary [161, 162] aliphatic amines at ambient or slightly elevated temperatures. The *anti*-Markovnikov addition of the amine moiety is favored (19) [160].



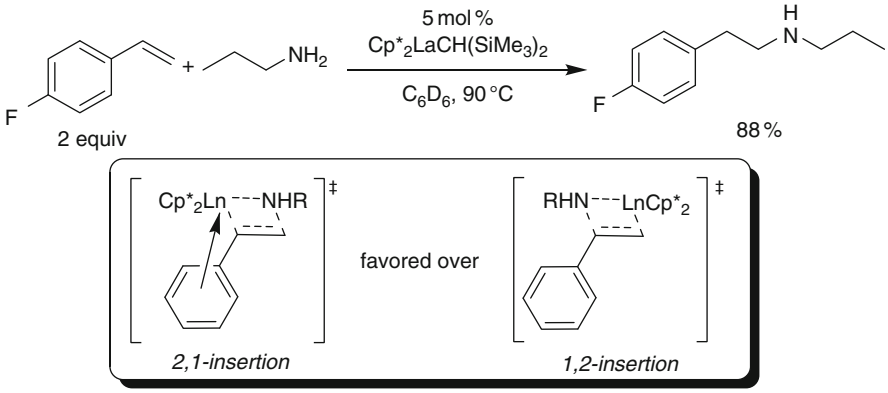
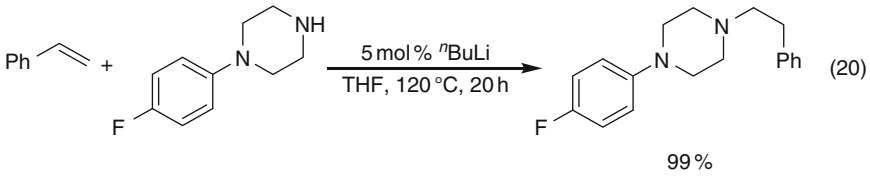
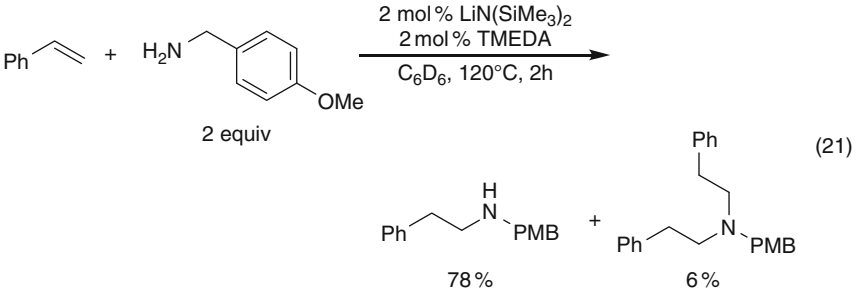


Fig. 12 Rare earth metal-catalyzed *anti*-Markovnikov hydroamination of vinyl arenes [20]

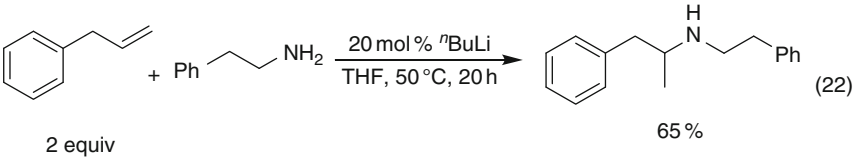
Lithium alkyls can also be used as homogeneous base-type catalysts for *anti*-Markovnikov addition of primary [163, 164] and secondary [163, 165, 166] amines to vinyl arenes. The reactions typically proceed in good to excellent yields to give β-phenethylamine derivatives (20) [165]. Unfortunately, ammonia does not exhibit the same reactivity as primary and secondary amines.



The simple lithium amide LiHMDS catalyzes the addition of aliphatic and (notably) aromatic amines to vinyl arenes [40]. The catalytic activity is increased by addition of TMEDA and the reaction can be carried out in bulk without additional solvent. More reactive primary aliphatic amines also form a bis-hydroamination product, although the formation of the latter may be suppressed by using an excess of amine (21). Less reactive aromatic amines and α- and β-substituted styrenes give the monohydroamination adducts selectively [40]. Other readily available alkali metal-based catalysts include NaH [166], *t*-BuOK [164, 167, 168] and CsOH [169].



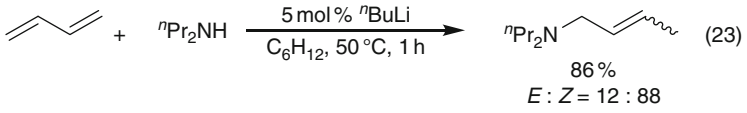
Although alkali metal amides cannot catalyze intermolecular hydroamination of higher unactivated alkenes, allylbenzene derivatives react smoothly via base-catalyzed isomerization into β-methyl styrene derivatives, which are active enough to form hydroamination products (22) [170].



5.2 *Hydroamination of Conjugated Dienes*

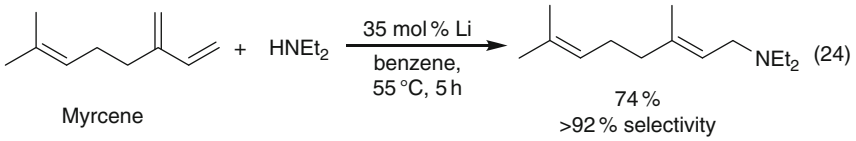
Conjugated dienes can serve as reactive substrates in both inter- and intramolecular hydroamination processes since the reactivity of the conjugated system is significantly higher than that of an isolated double bond.

The hydroamination of dienes with basic primary and secondary amines can be achieved with a variety of catalysts including alkali metals and their readily available derivatives. Reactions of acyclic 1,3-dienes catalyzed by alkali metals [159, 160, 171], metal hydrides [172], and metal amides (generated from metal alkyls) [163, 173, 174] result in regioselective formation of the sterically less hindered 1,4-addition product in most cases (23) [174]. Primary aliphatic amines are capable of performing double hydroamination in these conditions, typically leading to complex mixtures of mono- and bis-allyl amines, whereas reactions with secondary amines are more practical [160].



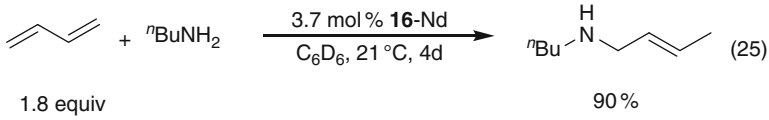
(23)

Isolated double bonds are significantly less reactive than the conjugated diene moiety which is illustrated by the base-catalyzed regioselective hydroamination of myrcene to form diethylgeranylamine (24) [171]. This reaction is performed industrially on a multi ton scale as part of the Takasago menthol synthesis [175].



(24)

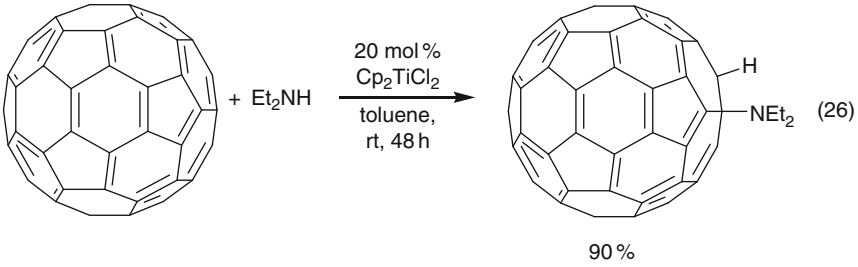
A few examples of rare earth metal-catalyzed diene hydroamination have been reported. The reaction apparently proceeds in line with base-catalyzed intermolecular hydroaminations to give the 1,4-addition product when using the *ansa*-neodymocene $Me_2Si(C_5Me_4)_2NdCH(SiMe_3)_2$ (**16**-Nd) (25) [20, 65].



(25)

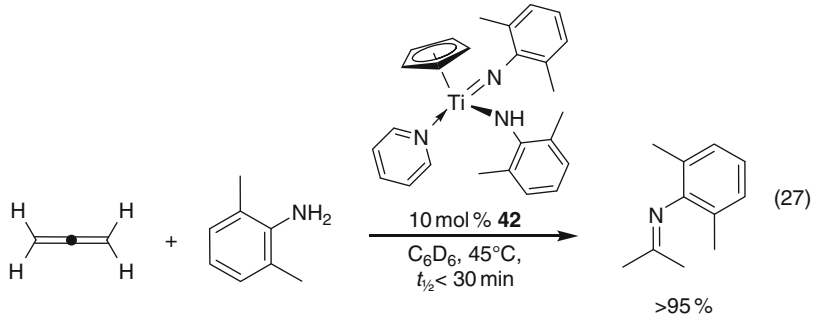
DFT-calculations suggest that the exclusive 1,4-regioselectivity results from regiospecific insertion and protonolysis steps (see also Sect. 3.3) [176].

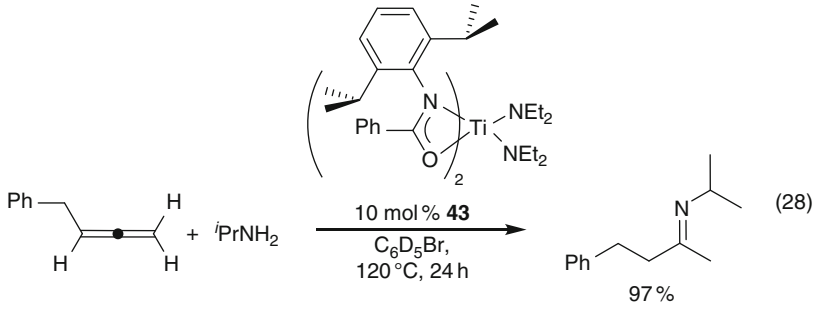
While the intermolecular hydroamination of butadiene derivatives with group 4 metal catalysts has not yet been reported, an interesting 1,2-addition of diethylamine to the Buckminsterfullerene C_{60}, which can indeed be seen as a conjugated polyene, was described (26) [177].

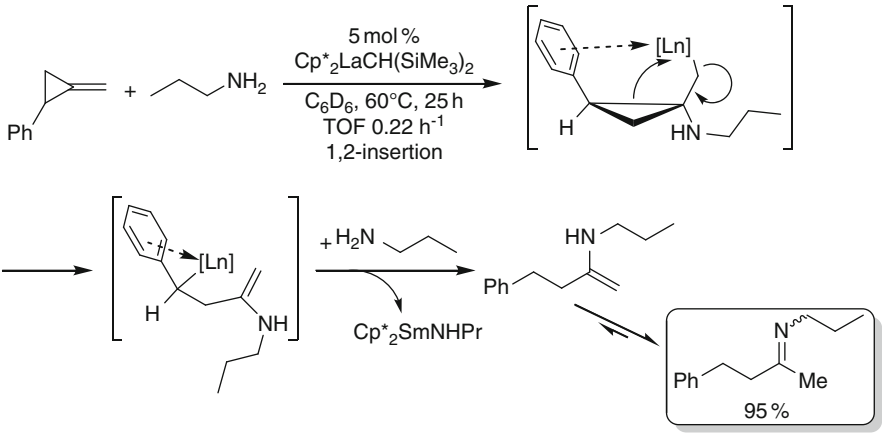


5.3 *Hydroamination of Allenes and Methylenecyclopropanes*

The intermolecular hydroamination of allenes is readily catalyzed by early transition metal complexes to yield imines. An addition of aromatic and aliphatic amines to allene requires high reaction temperatures (90–135°C) and long reaction times (1–6 days) when mediated by zirconocene- [41] and tantalum-imido [178] catalysts. The more efficient titanium half-sandwich imido-amide complex **42** operates under significantly milder reaction conditions (27) [179]. Because the metal-imido species are prone to dimerization, sterically more hindered aliphatic and aromatic amines are more reactive. Simple, sterically unencumbered aliphatic amines add to allenes in the presence of the bis(amidate) titanium complex **43** (28), although higher reaction temperatures are required [180].







Scheme 14 Intermolecular hydroamination of phenylmethylenecyclopropane [20]

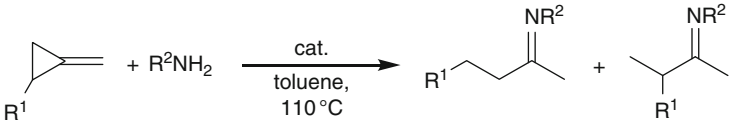
The intermolecular hydroamination of allenes with rare earth, alkaline earth and alkali metal catalysts has not been reported. However, another interesting and versatile class of unsaturated substrates closely related to allenes has been reported to undergo rare earth metal-catalyzed intermolecular hydroamination. Methylenecyclopropanes utilize the ring strain of the cyclopropane ring as the driving force for the reaction. Ring opening of the unsymmetrical phenylmethylenecyclopropane proceeds with high regioselectivity to generate the linear product predominantly (Scheme 14) [20].

Group 4 metal complexes, such as $Ti(NMe_2)_4$, $Zr(NMe_2)_4$, and the bis(aminopyridinato) complex **45**, were shown to catalyze the intermolecular ring-opening hydroamination of methylenecyclopropanes (Table 9) [181]. Analogous to rare earth metal-based catalysts, hydroamination reactions involving the unsymmetrical phenylmethylenecyclopropane (PhMCP) led to the linear regioisomer **44a** (R^1 = Ph) when titanium-based catalysts were applied. The sterically more encumbered **45** exhibited superior activity in case of sterically undemanding aliphatic and aromatic amines, while $Ti(NMe_2)_4$ exhibited better activity with bulky anilines. Interestingly, $Zr(NMe_2)_4$ was not only significantly less reactive than its titanium analog, but also exhibited opposite regioselectivity in the ring-opening to yield the branched isomer **44b** predominantly. The authors attributed this phenomenon to a different protonolysis/ring-opening pathway in case of the zirconium catalyst [181].

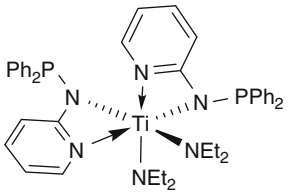
5.4 Hydroamination of Alkynes

A variety of catalyst systems have been developed for the facile intermolecular hydroamination of alkynes, in particular employing early transition metal catalysts based on group 4 metals (Fig. 13). Important issues such as reactivity, reaction

Table 9 Ring-opening hydroamination of methylenecyclopropanes with group 4 metal catalysts [181]



44a **44b**



45

R^1	R^2	Cat.	[cat.]/[s], mol%	*t*, h	**44a**:**44b**	Yield, %
H	Et	**45**	2	36	–[a]	90
Ph	^{n}Bu	$Ti(NMe_2)_4$	2	258	90:10	25
Ph	^{n}Bu	**45**	5	20	100:0	90
Ph	Ph	$Ti(NMe_2)_4$	2	24	83:17	100
Ph	Ph	**45**	5	17	87:13	83
Ph	Mes	$Ti(NMe_2)_4$	2	96	86:14	100
Ph	Mes	$Zr(NMe_2)_4$	2	380	8:92	89
Ph	2,6-^{i}Pr$_2$C$_6$H$_3$	$Ti(NMe_2)_4$	2	22	80:20	100
Ph	2,6-^{i}Pr$_2$C$_6$H$_3$	$Zr(NMe_2)_4$	2	215	29:71	100
Ph	2,6-^{i}Pr$_2$C$_6$H$_3$	**45**	5	120	100:0	24

[a]For R^1 = H: **44a** = **44b**

scope, and selectivity were addressed using multiple approaches, which has been extensively reviewed in recent general [5] and specialized [4, 192, 193] reviews.

The first group 4 metal catalysts for alkyne hydroamination were introduced in 1992 [41, 194, 195]. The bis(amido)zirconocene complex **46** [41] was restricted to bulky arylamines, and the reaction proceeded rather sluggishly (Table 10). Titanium catalysts are significantly more reactive than zirconium analogs, and even the homoleptic tetraamide $Ti(NMe_2)_4$ [196, 197], which lacks a bulky spectator ligand, showed enhanced activity in the hydroamination with aniline. However, aliphatic amines, including ^{t}BuNH$_2$ gave poor or no yield when using $Ti(NMe_2)_4$ [196, 197]. The readily available titanocene Cp_2TiMe_2 (**47**) reacted efficiently with sterically demanding aliphatic and aromatic amines with good yields but sterically less demanding amines, such as *n*-hexyl amine or benzyl amine reacted very sluggishly, supposedly due to facile formation of bridging imido dimers [182]. The metallocene **47** exhibited a significant induction period in catalytic hydroamination reactions and the presence of free cyclopentadiene was observed in the reaction

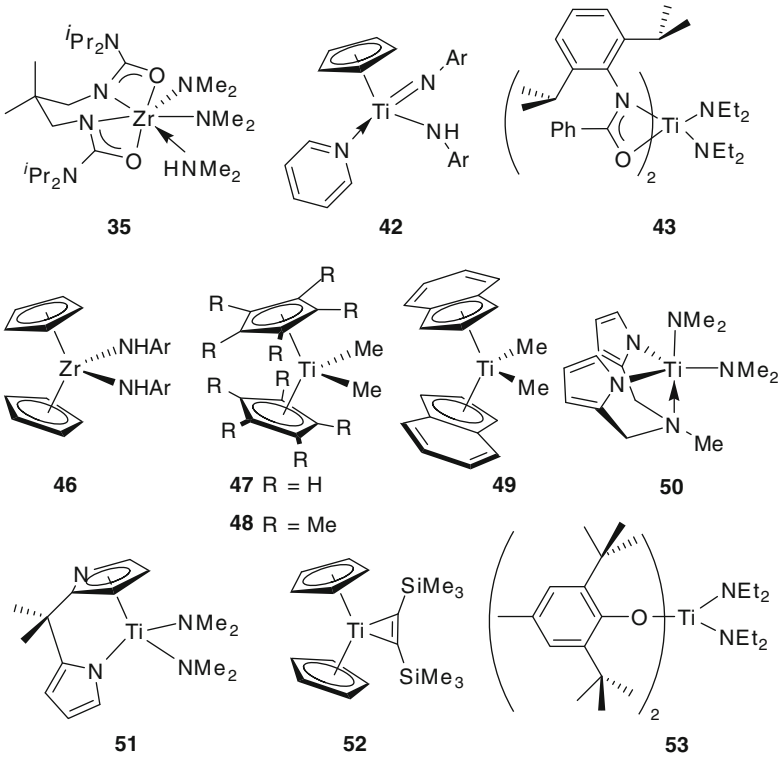
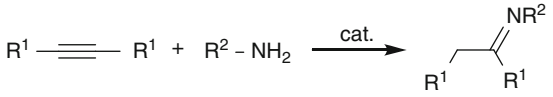


Fig. 13 Group 4 metal catalysts for alkyne hydroamination (Ar = 2,6-$Me_2C_6H_3$) [41, 179, 182–191]

mixture. The monocyclopentadienyl amido-imido complex **42** was obtained from the reaction of **47** with 2,6-dimethylaniline followed by addition of pyridine [179]. **42** was significantly more reactive without any induction period, suggesting that **42** could resemble the actual resting state also for the metallocene precatalyst **47** [179]. The sterically more encumbered titanocene **48** showed superior reactivity compared to **47** for the less bulky amines, such as *n*-propylamine; however, **48** was not applicable to bulkier aliphatic and aromatic amines [183]. Further optimization of the ligand structure led to the bis(indenyl) complex **49**, which appears to be the most versatile catalyst of the titanocene family [184] applicable even to the sterically least hindered amines, such as ethyl and methylamine [185].

Reactions of unsymmetric internal alkynes are more challenging, since two hydroamination products can be formed. The feasibility to control regioselectivity depends on the steric properties of both substrate and catalyst and a universal regioselective catalyst remains to be elaborated. When anilines are employed as reactants, high *anti*-Markovnikov selectivity is obtained with titanocene catalysts **47** and **48** (Table 11) [182, 183] while aliphatic amines gave poor results. Again, the bis(indenyl)titanium catalyst **49** showed superior *anti*-Markovnikov selectivity

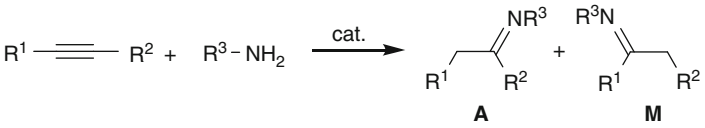
Table 10 Group-4-metal-catalyzed hydroamination of symmetric internal alkynes



R^1	R^2	Cat.	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	Ref.
Ph	2,6-$Me_2C_6H_3$	**46**	3	120	312	60[a]	[41]
Ph	Ph	$Ti(NMe_2)_4$	10	75	57	92[b]	[196, 197]
Ph	Ph	**47**	3	100	72	92[b]	[182]
Ph	Cy	**47**	3	100	72	86[c]	[182]
Ph	2,6-$Me_2C_6H_3$	**42**	3	75	–[d]	95[a]	[179]
Ph	^{n}Pr	**48**	6	114	4	86[b]	[183]
Ph	^{n}Pr	**49**	5	105	3	89[b]	[184]
Ph	Me	**49**	5	105	7	92[c]	[185]
Ph	^{t}Bu	**49**	5	105	5	84[b]	[184]
^{n}Pr	2,6-$Me_2C_6H_3$	**49**	5	105	24	92[b]	[184]

[a]Enamine tautomer
[b]Yield of ketone after hydrolysis with HCl
[c]Yield of amine after reduction
[d]$t_{½}$ = 15 min

Table 11 Group-4-metal-catalyzed hydroamination of unsymmetric internal alkynes



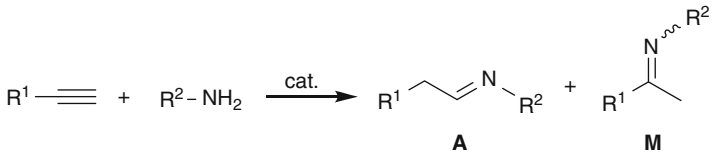
R^1	R^2	R^3	Cat.	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	**A**:**M**	Ref.
Ph	Me	Ph	**47**	1	100	40	99[a]	100:0	[182]
Ph	Me	4-MeC_6H_4	**48**	6	114	24	92[b]	97:3	[183]
Ph	Me	Bn	**48**	6	114	24	94[b]	75:25	[183]
Ph	Me	Bn	**49**	5	105	2	76[b,c]	97:3	[184]
Ph	C_3H_5	C_5H_9	**49**	5	105	24	89[b]	95:5	[184]
Ph	Me	4-MeC_6H_4	**49**	5	105	24	99[b]	98:2	[184]

[a]Yield of ketone after hydrolysis with HCl
[b]Yield of amine after reduction
[c]Slow amine addition

for aromatic and aliphatic amines of various steric bulk. Slow amine addition is beneficial for both reactivity and regioselectivity [184].

Terminal alkynes are in general more reactive than their internal analogs, and even $Ti(NMe_2)_4$ can serve as a catalyst in some cases providing high regioselectivity under relatively mild reaction conditions (Table 12) [196, 197]. However, the di(pyrrolyl) amine complex **50** (Fig. 13) was a more generally applicable

Table 12 Group-4-metal-catalyzed hydroamination of terminal alkynes

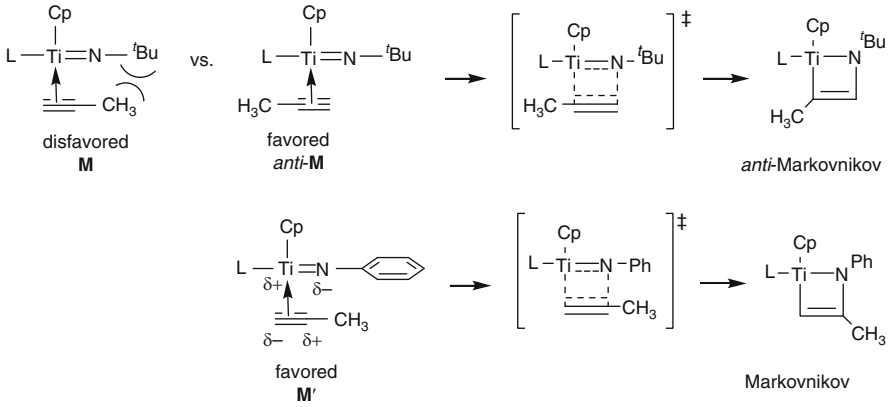


R^1	R^2	Cat.	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	**A**:**M**	Ref.
Ph	Ph	$Ti(NMe_2)_4$	10	75	2	49[a]	1:2	[196, 197]
Ph	^{t}Bu	$Ti(NMe_2)_4$	10	75	10	53	50:1	[196, 197]
^{n}Bu	4-MeC_6H_4	$Ti(NMe_2)_4$	10	75	2	87[b]	1:4	[196, 197]
^{n}Bu	Ph	**50**	10	75	6	90[b]	1:50	[186, 187]
^{n}Bu	C_6F_5	**50**	10	75	72	51[b]	1:50	[186, 187]
^{n}Bu	Cy	**50**	10	75	72	73[b]	1:2	[186, 187]
Ph	Cy	**51**	5	25	0.17	54	1:20	[188]
^{n}Bu	Ph	**51**	5	25	0.08	57	1:40	[188]
^{n}Bu	^{t}Bu	**52**	2.5	85	2	90	99:1	[189]
^{n}Bu	^{s}Bu	**52**	5	85	24	86	3:1	[189]
^{n}Bu	Ph	**52**	5	100	24	94	1:3	[189]
$^n C_6H_{13}$	^{s}Bu	**53**	10	100	24	98	10:90	[190]
$^n C_6H_{13}$	Ph	**53**	10	100	24	99	22:78	[190]
^{n}Bu	^{t}Bu	**43**	5	65	6	82[a]	49:1	[191]
^{n}Bu	Bn	**43**	5	65	24	88[a]	49:1	[191]

[a]Yield of amine after reduction
[b]After acid hydrolysis

catalyst than $Ti(NMe_2)_4$ with excellent Markovnikov selectivities for the hydroamination of terminal alkynes [186, 187]. The substrate scope included sterically less demanding amines, such as benzyl amine, and even the electron deficient pentafluoroaniline. However, the isopropylidene-linked di(pyrrolyl) complex **51** showed far superior reactivity, catalyzing the rapid and exothermic addition of aniline and cyclohexylamine to terminal alkynes with Markovnikov selectivity at room temperature [188].

The *anti*-Markovnikov hydroamination of terminal alkynes, which is providing relevant aldimine derivatives, has been studied intensively and a range of catalysts have been developed. The η^2-alkyne titanocene $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$ (**52**) was found to efficiently catalyze the *anti*-Markovnikov addition of the sterically demanding *tert*-butyl amine to terminal aliphatic alkynes with high (>98%) regioselectivity [189]. Sterically less demanding aliphatic amines also produced *anti*-Markovnikov adducts, albeit with reduced regioselectivity, while aromatic amines led predominantly to the Markovnikov product in which the regioselectivity correlated with the steric demand of the aniline derivative. A computational study revealed that the regioselectivity is determined by the relative stability of the imido



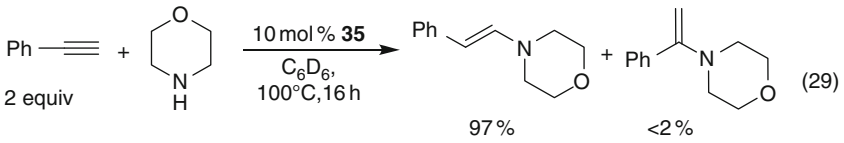
Scheme 15 Reaction pathway of [2 + 2] cycloaddition leading to predominantly *anti*-Markovnikov addition for sterically demanding amines and Markovnikov addition for aromatic amines

alkyne complex that precedes the [2 + 2] cycloaddition step (Scheme 15) [198]. The preference for *anti*-Markovnikov addition for *tert*-butyl amine can be based on a repulsive steric interaction of the *tert*-butyl substituent with the aliphatic substituent of the alkyne in the imido alkyne intermediate **M** leading to the Markovnikov product. The Markovnikov regioselectivity for aromatic amines on the other hand is based on the favorable alternating positive and negative charges in the Markovnikov imido alkyne intermediate **M'**.

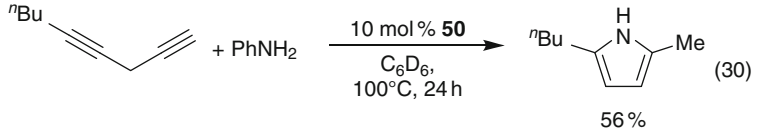
The sterically demanding bis(aryloxide) catalyst system **53** was found to be a highly efficient catalyst for the Markovnikov addition of sterically nonhindered amines, such as benzyl amine, *n*-alkylamines, *sec*-butyl amine, cyclooctyl amine, or aniline derivatives [190, 199, 200]. A broad screening of catalysts with various aryloxide ligands revealed that the regioselectivity can be reversed from high Markovnikov selectivity to high *anti*-Markovnikov selectivity by decreasing the steric demand of the aryloxide ligand [190].

The increased Markovnikov selectivity in the hydroamination of aliphatic terminal alkynes with aniline derivatives seems to be universal for a number of titanium-based hydroamination catalysts, such as Ind_2TiMe_2 (**49**) [184], the di(pyrrolyl) amine complex **50** [186, 187], and the di(pyrrolyl)methane complex **51** [188]. The bis(amidate) titanium complex **43** exhibited enhanced catalytic activity compared to titanocene catalysts, thus combining high *anti*-Markovnikov selectivity with high catalytic activity [191].

It is noteworthy that all group-4-metal-based catalysts described above can only be used for primary amines, as opposite to most late transition metal-based systems. While the stoichiometric reaction of $Ti(NMe_2)_4$ with phenylacetylene was shown to produce some enamine hydroamination product [196], a catalytic process was only facilitated using the tethered zirconium bis(ureate) complex **35** (29) [57].



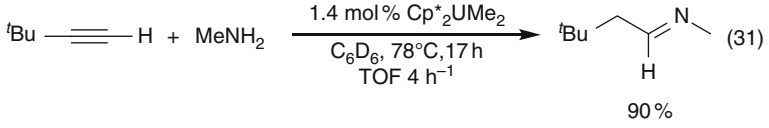
Poly(unsaturated) substrates can be used for sequential hydroamination/5-*endo*-cyclization reactions, which can be formally – but not mechanistically – seen as sequential inter/intramolecular hydroamination, to yield heterocyclic products, e.g., pyrroles from 1,4-diynes (30) [201].

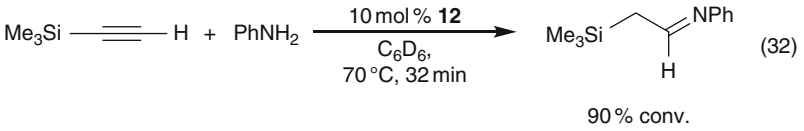


Cyclization reactions triggered by intermolecular alkyne hydroamination reactions provide straightforward access to structurally diverse heterocyclic motifs as summarized in a recent general [5] and specialized [202] review.

Only a few studies of group-5-metal-catalyzed alkyne hydroamination reactions have been reported. The imido-bridged dimer $[V(\mu^2\text{-NPh})(NMe_2)_2]_2$ [203], the tantalum alkyl imido complex $[(Me_3CCH_2)_3Ta = NCMe_3]$ [178, 204], and its cationic analog $[Bn_2Ta = NCMe_3]^+[B(C_6F_5)_4]^-$ [178, 204] were shown to be active hydroamination precatalysts, although the reactivity is significantly lower than that of group 4 metal catalysts. Mechanistic studies on tantalum catalysts were unable to confirm an imido-mechanism analogous to group 4 metals [205].

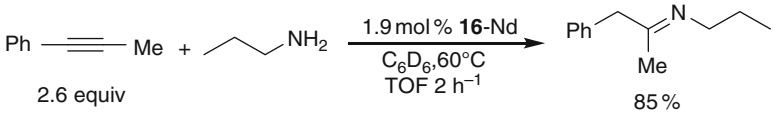
A number of actinide complexes have been investigated with respect to their catalytic activity in the intermolecular hydroamination of terminal alkynes with primary aliphatic and aromatic amines [98, 206–209]. Secondary amines generally do not react and the reaction is believed to proceed via an metal-imido species similar to that of group 4 metal complexes. The reaction of $Cp^*_2UMe_2$ with sterically less-demanding aliphatic amines leads exclusively to the *anti*-Markovnikov adduct in form of the *E*-imine (31) [207]; however, sterically more demanding amines, e.g., *t*-$BuNH_2$, result in exclusive alkyne dimerization. The ferrocene-diamido uranium complex **12** (Fig. 4) catalyzes the addition of aromatic amines very efficiently (32) [98].





(32)

Organolanthanide catalysts were explored less broadly compared to group 4 metal complexes. Intermolecular hydroamination of internal alkynes with inequivalent substituents gives the corresponding imines in a regioselective fashion (33) using the *ansa*-lanthanocene $Me_2Si(C_5Me_4)_2NdCH(SiMe_3)_2$ (**16**-Nd) [20, 65].



(33)

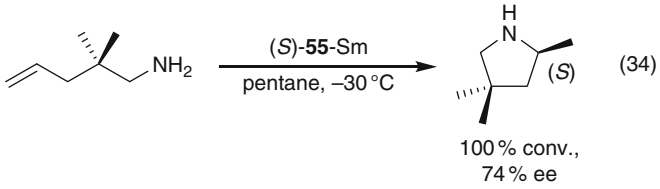
6 Asymmetric Hydroamination

The asymmetric hydroamination constitutes a facile and atom-economical approach to chiral amines. The rational design of efficient, configurationally stable and highly selective catalysts has become an area of intense research activity. Significant progress has been made in the area of intramolecular enantioselective hydroamination, while intermolecular hydroamination remains highly challenging [8–15, 210, 211].

6.1 Intramolecular Hydroamination of Alkenes

6.1.1 Chiral Rare Earth Metal Catalysts

Chiral C_1-symmetric lanthanocenes (Fig. 14) have achieved enantioselectivities of up to 74% ee (34) in various intramolecular hydroamination reactions [72, 212, 213]. Complexes **54**–**56** are better suitable for the formation of five-membered rings, while complexes **57** are optimized for six-membered ring formation (35) thanks to the extended wingspan of the octahydrofluorenyl ligand.



(34)

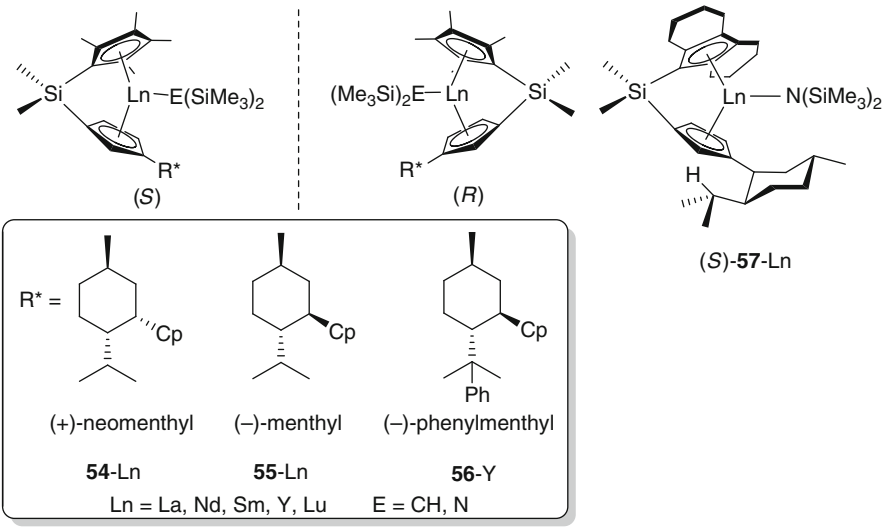
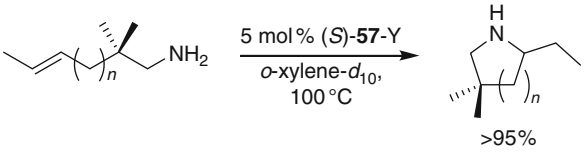


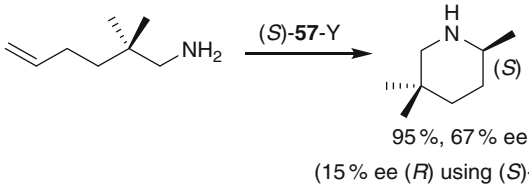
Fig. 14 C_1-symmetric chiral lanthanocene catalysts for asymmetric hydroaminations (R* = (+)-neomenthyl, (−)-menthyl, (−)-phenylmenthyl); E = N, CH) [72, 212, 213]

Table 13 Asymmetric hydroamination of internal alkenes [27]



n	TOF[a], h^{-1}	% ee
1	0.07	26 (+)
2	0.30	58 (−)

[a]TOF = turnover number per hour



(35)

The asymmetric hydroamination of internal 1,2-disubstituted alkenes is much less feasible and requires significantly harsher reaction conditions. The formation of pyrrolidines and piperidines often proceeds with comparable rates (Table 13), contrasting the general trend of significant faster five-membered ring formation

observed with terminal aminoalkenes [27]. Despite these harsh reaction conditions, moderate enantioselectivities of up to 58% ee at 100°C (up to 68% ee at 60°C) have been observed.

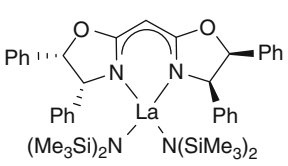
Unfortunately, the chiral lanthanocenes undergo facile epimerization under the conditions of catalytic hydroamination via reversible protolytic cleavage of the metal cyclopentadienyl bond [27, 72, 213, 214] leading to an equilibrium mixture of the two possible diastereomeric complexes. Thus, the enantioselectivity of product formation is limited by the catalyst's epimeric ratio in solution and the absolute configuration of the hydroamination product is independent of the diastereomeric purity of the precatalyst.

This limitation of chiral cyclopentadienyl-based hydroamination catalysts has stimulated the development of a large number of cyclopentadienyl-free rare earth metal-based catalyst systems [67, 68, 73, 121, 122, 215–239]. A detailed discussion of the large number of catalytic systems is beyond the scope of this review and the interested reader should refer to one of the comprehensive reviews on this topic [9–14]. Some prominent catalyst systems are shown in Fig. 15 and a brief survey of catalytic results is listed in Table 14.

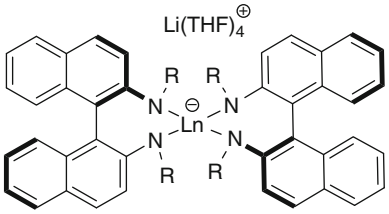
A variety of bisoxazolinato rare earth metal complexes such as **58** have been studied with regard to their hydroamination/cyclization catalytic activity [219]. The precatalysts show similar enantioselectivity and only slightly reduced catalytic activity when prepared in situ from $[La\{N(SiMe_3)_2\}_3]$ and the bisoxazoline ligand. In this ligand accelerated catalyst system, the highest rates were observed for a 1:1 metal to ligand ratio.

Based on a molecular modeling study, the preferred formation of the (*R*) pyrrolidine product was explained by an approach of the alkene to an empty equatorial coordination site of the bisoxazolinate complex with the amide being bound in the apical position (Fig. 16). The approach of the alkene to an apical coordination site with an equatorial La–N bond is expected to slightly favor formation of the (*S*) enantiomer. Interestingly, catalysts with aliphatic substituents (^{i}Pr, ^{t}Bu) in the 4-position of the bisoxazolinate ligand produced products with opposite configuration, potentially due to a change in the mode of approach of the alkene moiety.

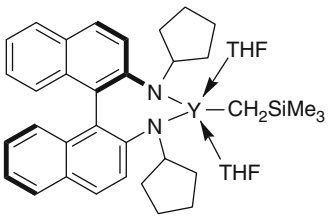
The ate-complexes $[Li(THF)_4][Ln\{(R)\text{-}1,1'\text{-}\{C_{10}H_6N(R)\}_2\}_2]$ ((*R*)-**59**; Ln = Yb, Y; R = ^{i}Pr (**a**), Cy (**b**), C_5H_9 (**c**)) [11, 14, 223–225, 227, 229, 230] are unusual hydroamination catalysts as they lack an obvious leaving amido or alkyl group that is replaced during the initiation step by the substrate. It is very likely that at least one of the amido groups is protonated during the catalytic cycle. The best catalytic results were obtained using a small rare earth metal (Yb) and a large cyclopentyl substituent on the diamidobinaphthyl ligand, but the low catalytic activity of **59** restrains them to activated *gem*-dialkyl substituted [69] aminoalkenes. A variety of diamidobinaphthyl alkyl and amido complexes, e.g., (*R*)-**60** and (*R*)-**61**, have been shown to exhibit better catalytic activity while retaining comparable enantioselectivities [227, 228, 231, 232]. The high activity of the bisalkyl ate-complex (*R*)-**61** allowed facile cyclization of 1,2-disubstituted aminoalkenes with enantioselectivities of up to 77% ee (36) at temperatures ranging from 40 to 110°C [233].



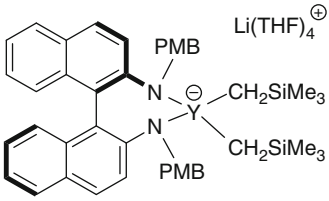
58



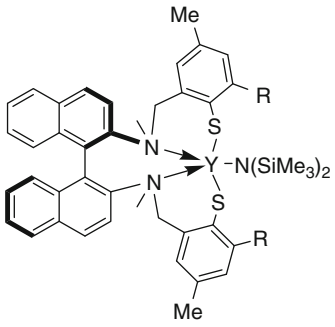
(*R*)-**59a** R = ^{i}Pr
(*R*)-**59b** R = Cy
(*R*)-**59c** R = C_5H_9



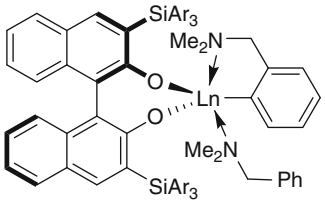
(*R*)-**60**



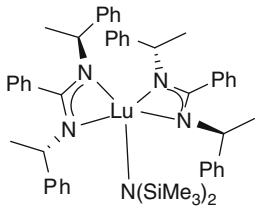
(*R*)-**61** PMB = $CH_2C_6H_5$-4-OMe



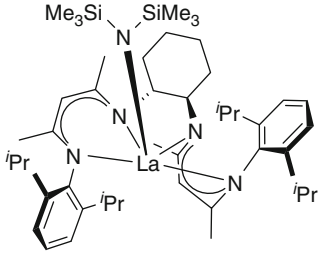
(*R*)-**62a** R = $SiMe_3$
(*R*)-**62b** R = $SiMe_2Ph$



(*R*)-**63a** Ar = Ph
(*R*)-**63b** Ar = 3, 5-$Me_2C_6H_3$



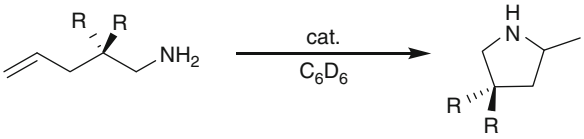
(*S*)-**64**



(*R*, *R*)-**65**

Fig. 15 Selected examples of post-metallocene rare earth metal catalysts for asymmetric hydroamination/cyclization of aminoalkenes [67, 121, 219, 220, 225, 227, 230, 233, 238, 239]

Table 14 Asymmetric intramolecular hydroamination of aminopentenes using post-metallocene rare earth metal catalysts



Cat.	R, R	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	% ee (config)	Ref.
58	H, H	5	23	~222[a]	>95	40 (*R*)	[219]
58	Me, Me	5	23	~0.8[b]	>95	67 (*R*)	[219]
58	Ph, Ph	1.3	23	~0.12[c]	>95	34 (*R*)	[219]
(*R*)-**59a**-Y	$-(CH_2)_5-$	7	25	20	quant.	67	[227]
(*R*)-**59b**-Yb	$-(CH_2)_5-$	6	25	18	94	65	[225]
(*R*)-**59c**-Yb	$-(CH_2)_5-$	6	25	20	90	87	[230]
(*R*)-**60**	Me, Me	6	25	144	94	77	[228]
(*R*)-**60**	$-(CH_2)_5-$	6	25	3.3	89	75	[228]
(*R*)-**62b**	H, H	5	60	8	95	81 (*S*)	[220]
(*R*)-**62a**	Me, Me	5	30	552	95	89 (*S*)	[220]
(*R*)-**63b**-Sc	H, H	5	22	17	93	90 (*S*)	[67]
(*R*)-**63a**-Sc	Me, Me	2	60	6	93	73 (*S*)	[67]
(*R*)-**63a**-Sc	Ph, Ph	2	25	0.6	94	95 (*S*)	[67]
(*S*)-**64**	Me, Me	5	60	35	92	75 (*S*)	[238]
(*R*,*R*)-**65**	Me, Me	9.6	25	~50[d]	>95	76 (*R*)	[239]

[a]TOF = 0.09 h^{-1}
[b]TOF = 25 h^{-1}
[c]TOF = 660 h^{-1}
[d]TOF = 0.2 h^{-1}

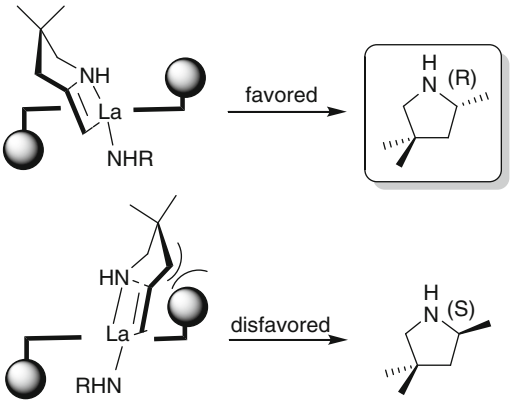
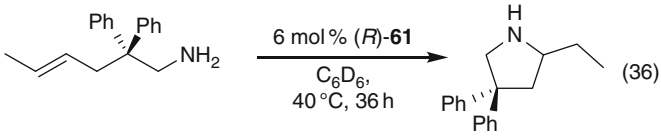


Fig. 16 Stereomodel for enantioselective hydroamination/cyclization using bisoxazolinate lanthanum catalyst **58** [219]. The structure of the bisoxazolinate ligand is simplified for clarity



83 % conv., 77 % ee

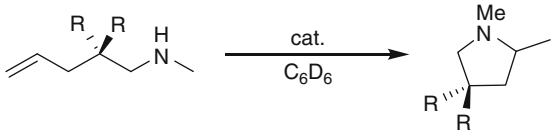
Good to high enantioselectivities for a wide range of aminoalkene substrates, including internal alkenes or secondary amines, were achieved using the in situ generated aminothiophenolate catalyst system (*R*)-**62** [220]. Variation of the steric demand of the silyl substituent attached to the thiophenolate moiety allowed facile fine-tuning of the enantiomeric excess, providing an increased selectivity with increasing steric hindrance. While the larger bite angle of the amino(thio)phenolate ligand is believed to improve enantiofacial differentiation as the chiral ligand reaches further around the metal center [217], the multidentate nature of the ligand also electronically saturates the metal center, effectively diminishing catalytic performance. Enantiomeric excess of up to 89% can be achieved at 30°C, although reactions at this temperature require a long period of time to reach completion.

Significantly higher catalytic activities were observed when more electron deficient ligand sets are employed. Binaphtholate complexes (*R*)-**63**, (Ln = Sc, Y, Lu) [67, 121] with sterically demanding tris(aryl)silyl substituents in the 3 and 3´ position show high catalytic activity at room temperature, comparable in magnitude to lanthanocene catalysts. Enantioselectivities of up to 95% ee were achieved in the hydroamination/cyclization of aminoalkenes, which are among the highest selectivities observed so far. The sterically demanding tris(aryl)silyl substituents in the diolate complexes play a pivotal role not only to achieve high enantioselectivities but also to prevent undesired complex aggregation [215]; furthermore, they reduce detrimental amine binding of the substrate and product to the catalytic active metal center [67]. Complexes with organophosphine oxide or sulfide substituents in the 3,3´-position of the binaphtholate ligand showed significantly reduced rates and low to moderate enantiomeric excess (up to 65% ee) [234], presumably as a result of organophosphine oxide/sulfide binding to the metal. Thus, the electronic environment for the catalytic active metal center needs to be carefully balanced.

Aminoalkenes with secondary amino groups generally cyclize slower and commonly also with diminished enantioselectivity in comparison to substrates with primary amino groups, presumably as a result of steric interference of the *N*-alkyl substituent in the stereodetermining cyclization transition state (Table 15). The diamidobinaphthyl complex (*R*)-**60** and related complexes seem to be an exception [240], as they tend to provide slightly higher enantioselectivities (up to 83% ee) and faster reaction rates for secondary aminoalkenes in comparison to the corresponding primary aminoalkenes (compare Tables 14 and 15).

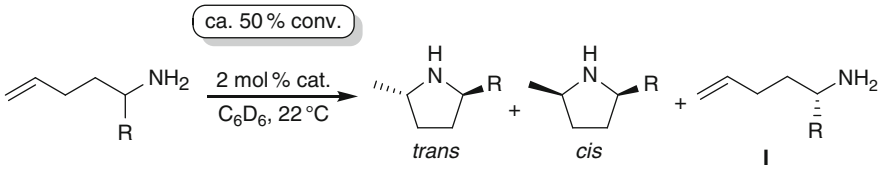
The binaphtholate complexes (*R*)-**63** were successfully applied in the efficient kinetic resolution of chiral aminoalkenes (Table 16) [67, 121, 122]. Racemic

Table 15 Asymmetric intramolecular hydroamination of aminoalkenes with a secondary amino group using post-metallocene rare earth metal catalysts



Cat.	R, R	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	% ee	Ref.
(*R*)-**60**	Me, Me	6	rt	0.17	95	80	[240]
(*R*)-**60**	$-(CH_2)_5-$	6	rt	0.17	95	83	[240]
(*R*)-**62**	H, H	5	60	30	95	69	[220]
(*R*)-**63b**-Sc	H, H	2	60	44	93	53	[67]

Table 16 Catalytic kinetic resolution of chiral aminopentenes



R	Cat.	*t*, h	Conv., %	*trans*:*cis*	% ee of recov. **I**	*f* [a]	Ref.
Me	(*R*)-**63b**-Y	26	52	13:1	80	16	[67, 121]
Cy	(*R*)-**63a**-Lu	23	47	8:1	51	6.0	[122]
Ph	(*R*)-**63a**-Lu	15[b]	52	≥ 50:1	83	19	[67]
Ph	(*R*)-**63a**-Lu	15[c]	64	n.d.	99	n.d.	[67]
4-ClC_6H_4	(*R*)-**63b**-Y	10[b]	51	≥ 50:1	80	19	[122]
4-$MeOC_6H_4$	(*R*)-**63a**-Y	8[b]	50	≥ 50:1	78	19	[67]

[a]Resolution factor
[b]At 40°C
[c]Using 1.3 mol% catalyst at 45°C. n.d. = not determined

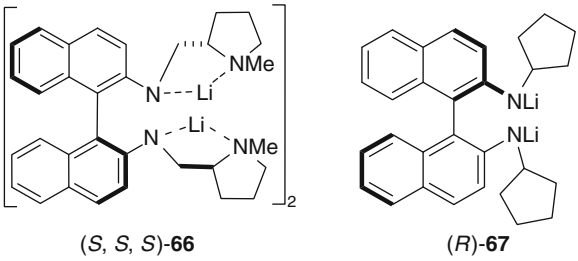
aminopentenes can be kinetically resolved with resolution factors *f* as high as 19. The resolution factor value depends dramatically on the nature of the substituent R. Mechanistic studies have revealed that diminished efficiencies in the kinetic resolution of aminoalkenes with aliphatic substituents are caused by an unfavorable state of the Curtin–Hammett-preequilibrium that favors the mismatching substrate–catalyst complex. In case of the significantly more efficient kinetic resolutions of aryl-substituted aminoalkenes, the matching substrate–catalyst complex predominates in the Curtin–Hammett preequilibrium [122].

6.1.2 Chiral Alkali Metal Catalysts

There have been only a limited number of studies on the application of chiral alkali metal complexes in asymmetric hydroamination of nonactivated aminoalkenes [135, 241, 242].

The proline-derived diamidobinaphthyl dilithium salt (*S*,*S*,*S*)-**66**, which is dimeric in the solid state and can be prepared via deprotonation of the corresponding tetraamine with *n*-BuLi, represents the first example of a chiral main-group-metal-based catalyst for asymmetric intramolecular hydroamination reactions of aminoalkenes [241]. The unique reactivity of (*S*,*S*,*S*)-**66**, (Fig. 17) which allowed reactions at or below ambient temperatures with product enantioselectivities of up to 85% ee (Table 17) [241, 243] is believed to derive from the close proximity of the two lithium centers chelated by the proline-derived substituents. More simple chiral lithium amides required significantly higher reaction temperatures and gave inferior selectivities.

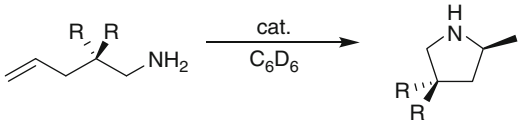
The diamidobinaphthyl dilithium salt (*R*)-**67** was generated in situ from the free diaminobinaphthyl ligand and 2.5 equiv. of $LiCH_2SiMe_3$ [135]. This system lacks a chelating sidearm and gave predominantly low enantioselectivities except for the *gem*-diphenyl-substituted aminopentene. Unfortunately, the cyclization of aminoalkenes seems to be limited to activated *gem*-dialkyl substituted [69] aminopentene



(*S*, *S*, *S*)-**66** (*R*)-**67**

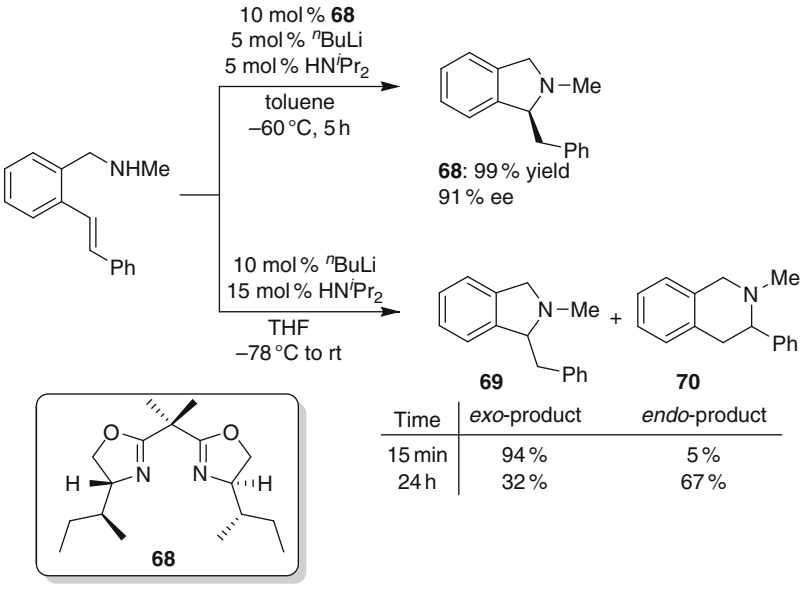
Fig. 17 Chiral lithium-based catalysts for asymmetric hydroaminations of aminoalkenes [135, 241]

Table 17 Lithium amide-catalyzed asymmetric hydroamination of aminopentenes



Entry	R, R	Cat.	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	% ee	Ref.
1	Me, Me	(*S*,*S*,*S*)-**66**	2.5[a]	22	45	93	67	[241]
2	$-(CH_2)_5-$	(*S*,*S*,*S*)-**66**	5[a]	20	2	82	74	[241]
3	$-(CH_2)_5-$	(*S*,*S*,*S*)-**66**	2[a]	−10	22	84	85	[243]
4	Ph, Ph	(*R*)-**67**	10	25	2	90	56	[135]

[a]Calculated with respect to the dimeric unit found in the pre-catalyst **66**



Scheme 16 Kinetic vs. thermodynamic control in the lithium-catalyzed cyclization of aminostilbenes [242]

substrates for catalysts **66** and **67**. However, a broader substrate scope can be found for the more reactive aminodienes (see Sect. 6.2).

The asymmetric hydroamination/cyclization of aminostilbenes has been studied utilizing chiral bisoxazoline lithium catalysts [242] and enantioselectivities reaching as high as 91% ee were achieved (Scheme 16). The reactions were performed in toluene at −60°C to give the *exo*-cyclization product **69** under kinetic control. However, the hydroamination/cyclization reaction in THF solution is reversible, producing the thermodynamically favored *endo*-cyclization product **70** when the reaction time was extended to 24 h.

Overall, although it has been clearly demonstrated that organolithium-catalyzed asymmetric hydroamination is accessible, further development is essential, in particular in terms of increasing the substrate scope.

6.1.3 Chiral Alkaline Earth Metal Catalysts

Similar to alkali metals, only few chiral alkaline earth metal complexes have been applied in asymmetric hydroaminations of nonactivated aminoalkenes [155, 244–248] and one of the greatest challenges has been the development of a chiral catalyst system that can resist facile ligand redistribution processes leading to achiral catalytically active species. Therefore, it is not too surprising that many systems are plagued with low enantioselectivities (Fig. 18, Table 18).

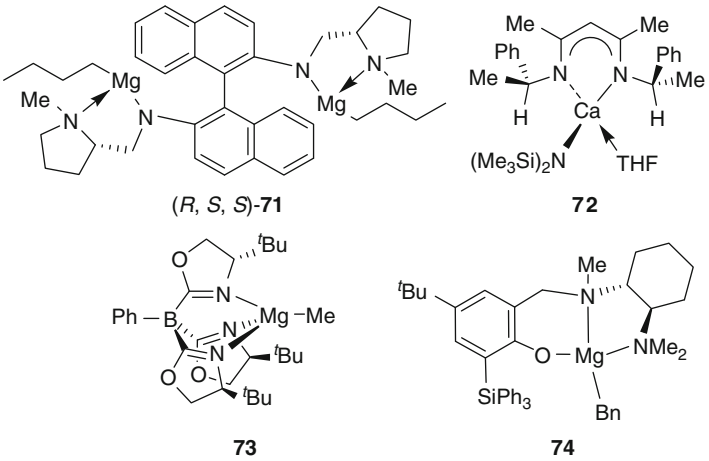
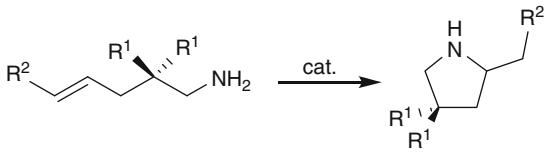


Fig. 18 Selected examples of chiral alkaline earth metal catalysts for asymmetric hydroamination/cyclization of aminoalkenes [155, 244–246]

Table 18 Alkaline earth-metal-catalyzed asymmetric hydroamination/cyclization of aminopentenes



Entry	R^1, R^1	R^2	Cat.	[cat.]/[s], mol%	*T*, °C	*t*, h	Yield, %	%ee (config)	Ref.
1	Ph, Ph	H	**71**	10	22	0.17	99	14 (*R*)	[244]
2	Ph, Ph	H	**72**	10	20	1	98	10 (*R*)	[245]
3	Me, Me	H	**73**	10	80	120	80	27 (*R*)	[246]
4	$-(CH_2)_5-$	H	**73**	10	60	26	93	36 (*R*)	[246]
5	Me, Me	H	**74**	5	22	10	97	79 (*S*)	[155]
6	$-(CH_2)_5-$	H	**74**	2	22	4.5	99	85 (*S*)	[155]
7	Ph, Ph	Ph	**74**	2	−20	12 h	98	93 (*S*)	[155]

The bis(amido) magnesium complex (*S*,*S*,*S*)-**71** [244] as well as the chiral diketiminato calcium compound **72** [245], which is a chiral analog of **21a** (Fig. 6), showed very low selectivity for the intramolecular hydroamination, apparently as a result of facile ligand redistribution reactions (Table 18, entries 1 and 2). Although the tris(oxazolinyl)borate **73** was reported to be stable, only low selectivities of up to 36% ee were obtained (Table 18, entry 4) [246]. In a marked contrast, the chiral magnesium phenoxyamine complex **74** [155] displayed selectivities of up to 93% ee as well as reactivity superior to that of the achiral analog **26** (Table 18, entries 5–7; compare with Table 4). This promising example illustrates that

reactivity and selectivity levels of rare earth metal catalysts can also be achieved with alkaline earth metal-based catalysts.

6.1.4 Chiral Group 4 Metal Catalysts

The development of group-4-metal-based catalysts for intramolecular hydroamination of alkenes has also led to several advanced systems for asymmetric hydroamination (Fig. 19). Most group 4 metal catalyst systems exhibit inferior reactivity and substrate scope (Table 19) in comparison to most rare earth metal- and alkaline earth metal-based catalyst systems. They typically require high catalyst loadings and elevated reaction temperatures. However, the recent development of zwitterionic zirconium catalysts with significantly improved reactivities and selectivities [60, 118] promises to close this gap.

The cationic aminophenolate complex (*S*)-**75** readily cyclizes secondary aminoalkenes with enantioselectivities of up to 82% ee (Table 19, entries 1–3) [62]. For catalyst solubility reasons, reactions are commonly performed in bromobenzene and require reaction temperatures of 100°C and catalyst loadings of 10 mol%. The mechanism of this cationic system is thought to proceed similar to the σ-bond metathesis mechanism of rare earth metal-based catalyst systems (Scheme 2) [61, 62].

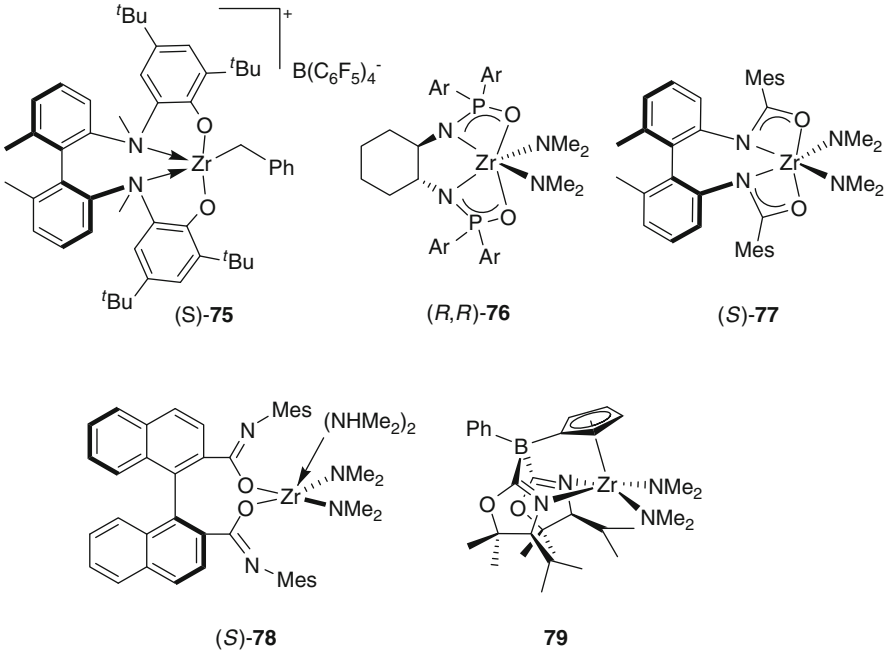
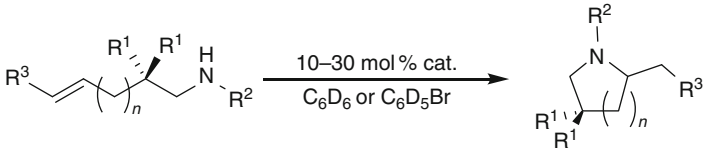


Fig. 19 Selected group 4 metal catalysts for asymmetric hydroamination of aminoalkenes (Mes = 2,4,6-$Me_3C_6H_2$; Ar = 3,5-$Me_2C_6H_3$) [60, 62, 249–254]

Table 19 Asymmetric hydroamination of aminopentenes catalyzed by zirconium complexes



Entry	Cat.	*n*	R^1	R^2	R^3	*T*, °C	*t*, h	Yield, %	% ee (config.)	Ref.
1	**75**	1	H	Me	H	100	4	100	60	[62]
2	**75**	1	Me	Me	H	70	48	70[a]	14	[62]
3	**75**	2	Me	Me	H	100	3	100	82	[62]
4	**76**	1	Me	H	H	115	24	95[b]	80 (*S*)	[249]
5	**76**	1	H	H	H	135	72	33[b]	62	[249]
6	**76**	1	Me	H	Ph	135	24	93[b]	62	[249]
7	**76**	2	Me	H	H	85	24	99[b]	51	[249]
8	**77**	1	Me	H	H	110	3	80	93 (*R*)	[250–252]
9	**77**	1	$-(CH_2)_5-$	H	H	110	3	96	82 (*R*)	[250–252]
10	**77**	1	Allyl	H	H	110	4.5	88	74 (*R*)	[250–252]
11	**77**	1	Ph	H	H	110	1.3	93	74 (*S*)	[250–252]
12	**77**	2	Me	H	H	110	3	n.r.	21	[250]
13	**78**	3	Ph	H	H	120	51	94	60	[254]
14	**79**	1	Me	H	H	rt	7	89	89 (*R*)	[60]
15	**79**	1	$-(CH_2)_5-$	H	H	23	1.25	88	90 (*R*)	[60]
16	**79**	1	$-(CH_2)_5-$	H	H	23	n.r.	n.r.	97 (*R*)[c]	[60]
17	**79**	1	Ph	H	H	−30[d]	120	>95	98 (*R*)	[60]
18	**79**	2	Ph	H	H	rt	30	65	46 (*R*)	[60]

[a]30% double bond isomerization
[b]Isolated as *N*-trifluoroacetamide
[c]Reaction of the *N*-deuterated substrate
[d]Reaction in THF-d_8. n.r. = not reported

Primary aminoalkenes do not react under these conditions, presumably due to a facile α-deprotonation of the catalytic active cationic metal-amido species leading to an unreactive metal-imido species [255]. The cationic catalyst systems are also prone to double bond isomerization via C–H activation (Table 19, entry 2) that can significantly diminish product enantioselectivity and yield [62].

In contrast to cationic group 4 metal hydroamination catalysts, their neutral counterparts will generally react only with primary aminoalkenes and reaction temperatures are typically higher (110–135°C). The chiral bis(phosphinic amido) zirconium complex (*R*,*R*)-**76** exhibits superior reactivity and enantioselectivity for the cyclization of primary aminoalkenes in comparison to a wide range of diamido, diolate, and aminoalcoholate titanium, zirconium, and hafnium complexes [249]. The cyclization of aminopentenes proceed with enantioselectivities as high as 80% ee, but formation of piperidines (Table 19, entry 7) is somewhat less selective. Unfortunately, mechanistic studies indicate that this catalyst system undergoes slow ligand redistribution reactions, leading to chiral catalytically inactive as well as achiral catalytically active species.

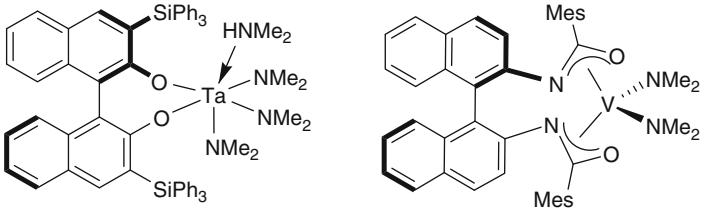
Higher enantioselectivities of up to 93% ee were achieved using the chiral bis(amidate) zirconium complex (*S*)-**77** (Mes = 2,4,6-$Me_3C_6H_2$), [250–253, 256], but again the high selectivities are limited to the formation of pyrrolidines, and unlike **75** and **76**, only *gem*-disubstituted substrates were reactive.

Although the binaphthalenedicarboxamide zirconium complex (*S*)-**78** [254] closely resembles the structure of complex (*S*)-**77**, the altered connectivity of the two amidate moieties to the axially chiral ligand backbone favors a more open κ^1 binding mode [257] of the *N*-mesityl amidate ligands that renders the metal more electron deficient and the catalyst system more active. The increased reactivity may be utilized to reduce catalyst loadings down to 0.5 mol% and reduce reaction temperatures to 70°C in the formation of pyrrolidines. Unfortunately, the more remote arrangement of the *N*-aryl substituents results in significantly diminished selectivities in comparison to **77**. However, the increased reactivity allows cyclization of a *gem*-diphenyl-substituted aminoheptene to give an azepane in 60% ee (Table 19, entry 13). This result is particularly noteworthy, as aminohexenes and aminoheptenes are frequently observed to undergo hydroaminoalkylation (via α–C–H activation) instead of hydroamination (via N–H activation) [120].

A significant breakthrough in both catalytic activity and selectivity was achieved with introduction of the chiral zwitterionic cyclopentadienyl-bis(oxazolidinyl) borate zirconium complex **79** [60], which enjoys enhanced reactivity like its achiral analog **33** (Fig. 8) [118] that allows reactions to be performed at temperatures as low as −30°C. Enantioselectivities of up to 98% ee were achieved for aminopentenes, but not for aminohexenes (Table 19, entries 14–18). The catalysts exhibit a significant primary kinetic isotope effect and an isotopic perturbation of enantioselectivity resulting in higher enantioselectivities for the *N*-deuterated substrates (Table 19, entry 15 vs. entry 16). However, despite an incredible reactivity improvement, **79** is also confined to *gem*-dialkyl-activated substrates and the unsubstituted aminopentene reacts only sluggishly even at 110°C.

6.1.5 Chiral Group 5 Metal Catalysts

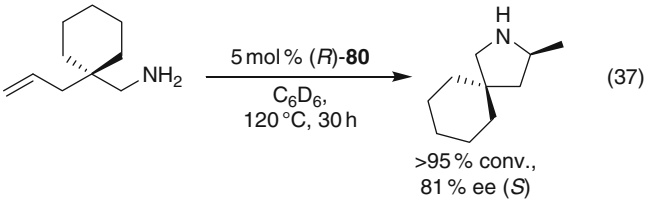
Asymmetric hydroamination of aminoalkenes catalyzed by binaphtholate tantalum complexes, e.g., **80** (Fig. 20), was reported recently [258]. Enantioselectivities of up



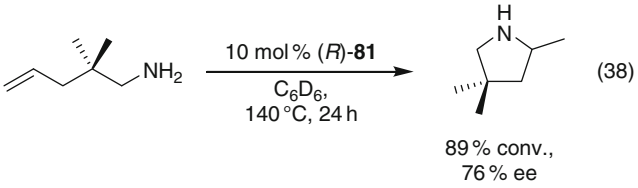
(*R*)-**80** (*R*)-**81**

Fig. 20 Selected group 5 metal catalysts for asymmetric hydroamination of aminoalkenes (Mes = 2,4,6-$Me_3C_6H_2$) [258, 259]

to 81% ee (37) were achieved with reactivity comparable to group 4 metal complexes. Similar to most group 4 metal catalysts only aminoalkenes with a primary amino group were cyclized. Interestingly, the tantalum and analogous niobium complexes catalyzed the asymmetric intermolecular hydroaminoalkylation of terminal alkenes with *N*-methyl anilines with great chemoselectivity and enantioselectivities of up to 80% ee [258]. The chiral bis(amidate) vanadium(IV) complex (*R*)-**81** showed also appreciable catalytic activity and enantioselectivity (38) [259]. It is unclear if the catalyst retains the +4 oxidation state and also related vanadium(III) complexes showed comparable activity. However, the corresponding bis(amidate) niobium(V) and tantalum(V) complexes were catalytically inactive.



(37)

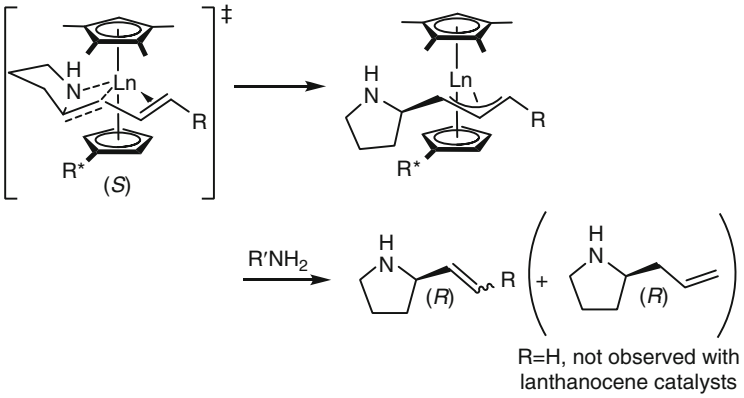


(38)

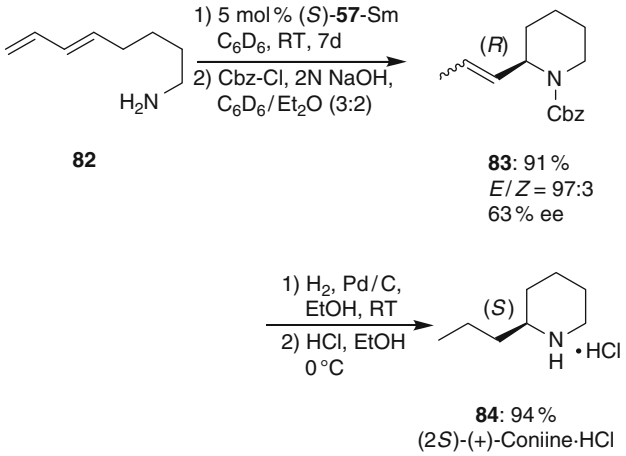
6.2 *Intramolecular Hydroamination of Dienes*

As discussed in Sect. 3.3, the hydroamination of 1,3-dienes is quite facile due to the transient formation of an η^3-allyl intermediate. Protonation usually leads to *E*/*Z* vinylpyrrolidines and vinylpiperidines, while allyl isomers are observed less frequently. Cyclizations with chiral lanthanocenes generally produce the *E* olefins with high *E* selectivity (*E*/*Z* $\geq$ 93:7, Scheme 17) [30, 31]. The reaction rates are higher for aminodienes in comparison to the corresponding aminoalkenes, despite increased steric encumbrance of the cyclization transition state. However, in most cases, the increased reactivity goes at the expense of enantioselectivity. The aminooctadiene **82** is an exception with 63% ee observed in a benzene solution at 25°C (71% ee in methylcyclohexane at 0°C) using (*S*)-**57**-Sm (Fig. 14), which gave facile access to (+)-coniine **84** after hydrogenolysis of the Cbz-protected vinylpiperidine **83** (Scheme 18) [31].

The hydroamination/cyclization of terminal aminodienes can also be catalyzed by chiral diamidobinaphthyl dilithium salts with up to 72% ee (Scheme 19) [134, 135]. Although the *E*/*Z* selectivity of the product is moderate in most cases, both diastereoisomers can be obtained with comparable enantiomeric excess.



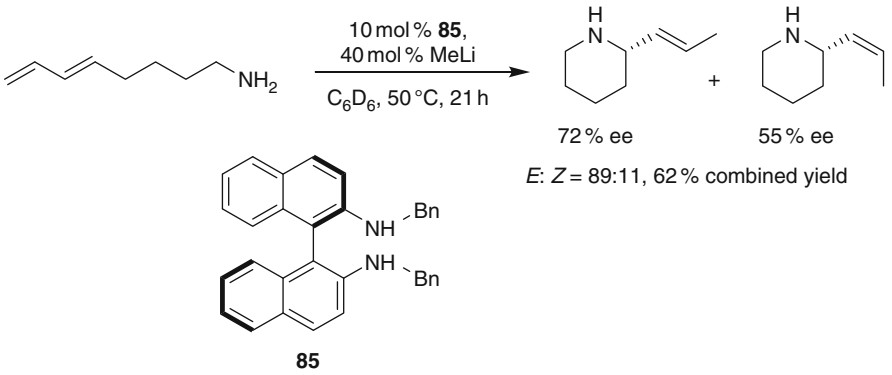
Scheme 17 Stereomodel for the lanthanocene-catalyzed hydroamination/cyclization of aminodienes. The silicon linker bridging the two cyclopentadienyl ligands was omitted for the sake of clarity



Scheme 18 Synthesis of (+)-coniine·HCl via enantioselective aminodiene hydroamination/cyclization [31]

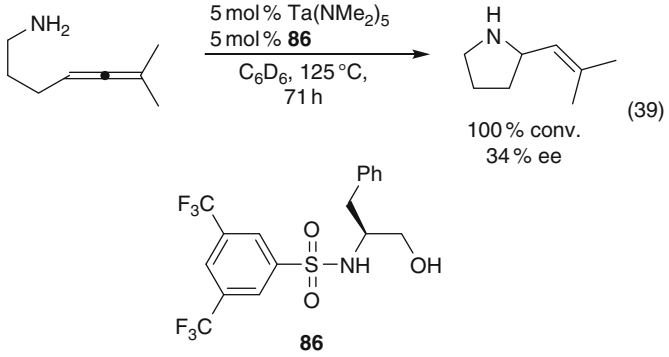
6.3 *Intramolecular Hydroamination of Allenes*

Although hydroamination of allenes can be easily achieved with group 4 and group 5 metal catalysts, the stereoselectivity of these systems is rather limited. Several attempts to perform asymmetric hydroamination/cyclization of aminoallenes employing chiral aminoalcohols [260, 261] and sulfonamide alcohols [262] as chiral proligands for titanium- and tantalum-based catalyst systems have produced vinyl pyrrolidines with low selectivities only. While the titanium catalysts were



Scheme 19 Lithium-amide catalyzed asymmetric hydroamination of an aminodiene [134, 135]

slightly more active, the tantalum catalyst system formed by reaction of $Ta(NMe_2)_5$ and one equiv of the sulfonamide alcohol **86** achieved the highest enantioselectivity of 34% ee. (39) [262].

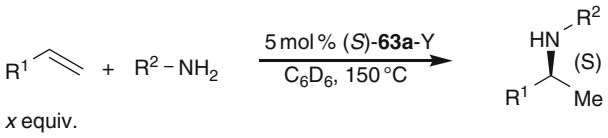


Thus, early transition metal catalyst systems have yet to reach the nearly perfect degree of stereoselectivity (up to 99% ee) achieved with late transition metal catalysts [263–266] and dithiophosphoric acids [267]. However, it should be noted that these systems are confined to *N*-protected (tosylates, ureas, carbamates) amines with reduced nucleophilicity, and the highly selective asymmetric hydroamination of aminoallenes with simple amino groups remains a challenge.

6.4 Intermolecular Asymmetric Hydroamination

The asymmetric intermolecular hydroamination is arguably the most challenging transformation in the context of hydroamination chemistry. Despite significant progress over the last two decades in the development of hydroamination catalysts in general, this particular area has seen little to no progress for early and late

Table 20 Asymmetric intermolecular hydroamination of unactivated alkenes



Entry	R^1	R^2	*x*	*t*, h	Yield, %	% ee
1	^{n}Pr	Bn	14	72	70	61
2	^{n}Bu	Bn	13	72	54	61
3	$PhCH_2CH_2$	$^cC_5H_9$	9	39	68	54
4	$PhCH_2CH_2$	PMB	10	48	67	56
5	Cy	Bn	12	96	<25	n.r.[a]

[a]n.r.- not reported

transition metal catalysts. The main reason lies in the challenge presented by intermolecular hydroamination of unactivated 1-alkenes (excluding ethylene) for which only a limited number of examples are known [20, 65, 152]. On the other hand, intermolecular hydroamination of alkynes or vinyl arenes is much more feasible (Sect. 5) but the products are commonly achiral.

Recently, the intermolecular Markovnikov addition of simple aliphatic primary amines to unactivated 1-alkenes was achieved using the binaphtholate yttrium complex **63a**-Y (Fig. 15) [68]. The reaction requires high temperatures and a 9–15-fold excess of the alkene was employed (Table 20). Secondary amines and internal alkenes are unreactive; moreover, sterically hindered terminal olefins also displayed significantly diminished reactivity (Table 20, entry 5). Enantioselectivities of up to 61% ee were achieved despite the harsh reaction conditions.

Although detailed mechanistic studies have not yet been performed, it is noteworthy that the reaction exhibits first order rate with respect to the concentration of catalyst and both reagents. This feature remarkably contrasts lanthanide-catalyzed intermolecular hydroamination of alkynes [20] and base-catalyzed intermolecular hydroamination of ethylene with secondary amines [152], which were both first order with respect to the concentration of the alkene/alkyne and the catalyst, but zero order in amine.

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Late Transition Metal-Catalyzed Hydroamination

Naoko Nishina and Yoshinori Yamamoto

Abstract This chapter describes late transition metal complexes-catalyzed hydroamination, the formal addition of an H–N bond across a C–C multiple bond. Late transition metal catalysis has been intensely developed in the hydroamination and additions of various kinds of amines to C–C multiple bonds have been achieved. The reaction pathways strongly depend on the choice of metal complexes, substrates, and reaction conditions. This chapter is organized primarily based on the difference in the mechanisms of hydroamination reactions, and in the scope section concise summary of the hydroamination reaction is shown.

Keywords Carbon–carbon multiple bonds · Hydroamination · Late transition metal · Mechanism · Nitrogen nucleophiles

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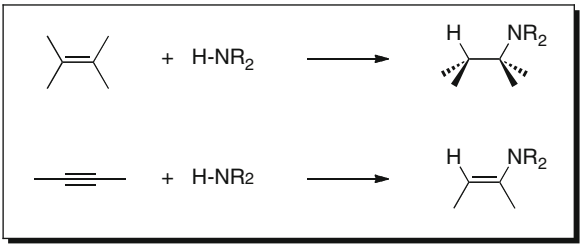
Abbreviations

Ar	Aryl
Bu	Butyl
cod	1,5-Cyclooctadiene
Cy	Cyclohexyl
d/D	Deuterium
dba	Dibenzylideneacetone
DPPPent	1,5-Bis(diphenylphosphino)pentane
Et	Ethyl
L	Ligand
M	Metal or molar (mol dm^{-3})
Me	Methyl
Nu	Nucleophile
P	Phosphorus atom in ligand
Pent	Pentyl
Ph	Phenyl
R	Organic substituent or alkyl
Tf	Trifluoromethanesulfonyl
Tol	Tolyl
Tol-BINAP	2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
Triphos	Bis(2-diphenylphosphinoethyl)phenylphosphine
Ts	*p*-Toluenesulfonyl (tosyl)
X	Halide
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Y	Counter anion

1 Introduction



Hydroamination, the formal addition of a H–N bond across a C–C multiple bond, is considered to be a highly valuable and atom-economical process for the preparation of nitrogen-containing compounds [1–12]. This chemistry has been widely studied with (1) organolanthanides, (2) alkali metals, (3) early [Ti, Zr] and (4) late [Ru, Rh, Ir, Ni, Pd, Pt, Cu, Au] transition metals, and (5) heterogeneous systems. Depending on the catalytic system, activation of either the C–C multiple bond or the N–H bond takes place; the former activation occurs in the case of (4) late transition metals, and the latter type takes place in the cases of metals (1)–(3) and also (4). Accordingly, the reactions catalyzed by late transition metals have possibility of taking the two different mechanisms, and the pathway strongly depends on catalysts, substrates, and reaction conditions. Additionally, there are two other important aspects of hydroamination; (a) the relative difficulty in achieving intermolecular hydroamination as compared to the intramolecular version and (b) the relative difficulty in achieving the hydroamination of alkenes compared to that of alkynes. To overcome the difficulty mentioned above and to make the mechanism much clearer, the hydroamination catalyzed by late transition metals is still one of the major topics and has been studied widely.

Consequently, the late transition metal-catalyzed hydroamination is focused in this chapter. In general, the late transition metal catalysts are relatively stable in air and tolerant of most of the polar functional groups. Accordingly, the catalysts are convenient to handle and perhaps applicable to many industrial syntheses.

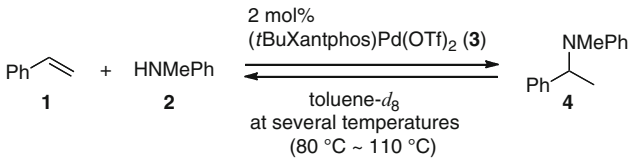
2 Thermodynamics in Direct and in Late Transition Metal-Catalyzed Addition

2.1 Direct Addition

Theoretical studies indicate that the direct addition of amines to C–C multiple bonds is feasible under standard conditions, because the process is slightly exothermic or approximately thermoneutral [13–18]. For the intermolecular direct addition of ammonia to ethylene, theoretically estimated free energy is −14.7 kJ/mol, but the

reaction is hampered by a high activation barrier caused by electrostatic repulsion between the electron-rich π-bonds and the amine nitrogen bearing a lone pair. For the [2+2] cycloaddition of N–H to alkenes, it would be an orbital symmetry-forbidden, and unfavorable due to the high energy gap between π(C=C) and σ(N–H). In addition to these facts, increasing temperature tends to shift the equilibrium of the reaction to the starting materials because of its highly negative entropy (−127.3 J/mol K). Therefore, nonactivated C–C multiple bonds and nonactivated amines are inert to the addition and a certain activation for the substrates is required. The hydroamination can be mediated or catalyzed by various metal complexes capable of decreasing the activation barrier.

2.2 *Late Transition Metal-Catalyzed Addition*

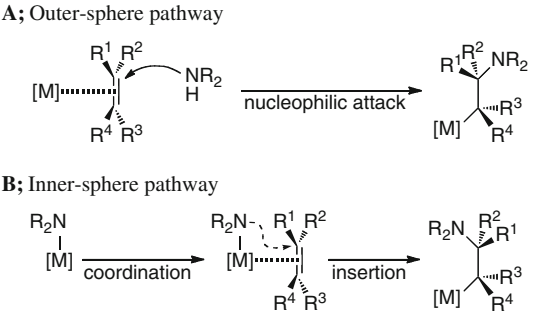


(1)

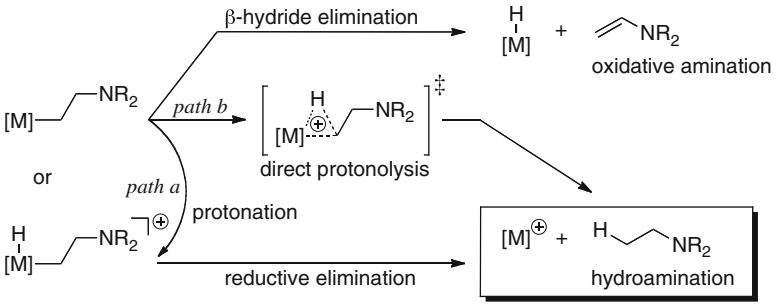
Recently, the thermodynamics for the additions of arylamines to vinylarenes have been directly measured in palladium complex catalysis (Eq. 1) [19]. The progress in reaction was monitored by ^{1}H NMR at several different temperatures, and the corresponding values of equilibrium constants are obtained. A van't Hoff plot using these values derives the values of enthalpy and entropy. For example, the addition and retro-addition reactions of styrene (**1**) with *N*-methylaniline (**2**) in the presence of (*t*BuXantphos)Pd(OTf)$_2$ (**3**) were monitored; for the addition process at 80 °C, the equilibrium constant was found to be $K = 1.5 \pm 0.1\ \mathrm{M}^{-1}$, the enthalpy $\Delta H = -10.0 \pm 0.8$ kcal/mol, and the entropy $\Delta S = -27 \pm 4$ cal/mol K, thus the free energy $\Delta G = -0.28 \pm 0.05$ kcal/mol. This means that the reaction has favorable enthalpy and unfavorable entropy, but its free energy balances to nearly zero. Due to a wide variety of reaction manners, it is not easy to give a generalized simple scheme which incorporates all the reaction types. However, in most cases energetic balances similar as mentioned above operate successfully pushing forward the catalytic cycle.

3 The Reaction Patterns and Mechanistic Details

The mechanism of hydroamination catalyzed by late transition metals is classified on the basis of the first elemental process, in which either a C–C multiple bond or an amine is activated by the metal center (Scheme 1) [1, 3, 12, 20]. In the former type (**A**, outer-sphere pathway), the nucleophilic attack of an amine occurs to the



Scheme 1 The outline of outer- and inner-sphere pathways



Scheme 2 The outline of M–C bond cleavage

coordinated C–C multiple bond from outside of the metal complex. In the latter type (**B**, inner-sphere pathway), the first process is the formation of metal amide species, which is followed by coordination and insertion of a C–C multiple bond. In either case, the catalytic cycle is terminated by the M–C bond cleavage. For late transition metal catalysis, hydroamination may occur through various pathways, and the detail strongly depends on the choice of metal catalysts, substrates, and reaction conditions. It is known that Lewis acidic metals of d^8 or d^{10} electron configuration exhibit particularly high catalytic efficiency [21–23].

The reaction patterns mentioned in the following sections are classified into two categories, **A** and **B**, and the studies on mechanistic details are mentioned in each section for better understanding.

As complementary information, the M–C cleavage process makes the understanding of the catalysis difficult because organometallic intermediates of late transition metals have strong tendency to undergo β-hydride elimination (Scheme 2). Actually, this type of reactions, oxidative amination, has been reported by rhodium and palladium catalysis [24–26]. To preferentially promote hydroamination, the undesired β-hydride elimination should be suppressed, and the use of chelate ligands is thought to be effective by preventing formation of any

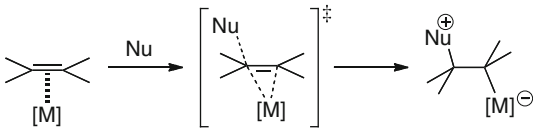
coordination sites at metal [27], though several reactions including reversible β-hydride elimination process are possible to release hydroamination product. Although the details are remaining ambiguous, the protonolysis of M–C bond is well studied by platinum complexes, and this process is thought to proceed by following either way [28, 29]: *path* (*a*), a stepwise protonation at the central metal of alkyl-M^{n+} species by using nonbonding d-orbitals to give alkyl-M^{n+2}-hydride species, which can be generated by aminometallation reaction discussed in Sect. 3.2.2, followed by reductive elimination or *path* (*b*), a concerted protonation at the σ-bonding molecular orbital of M–C bond in nonoxidative manner often called as direct protonolysis.

3.1 C–C Multiple Bond Activation Pathway

3.1.1 Outer-Sphere Pathway

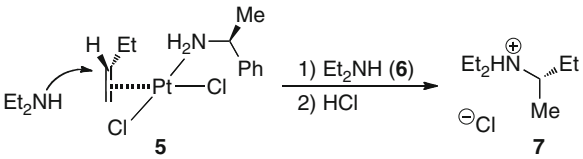
There are many examples in which late transition metal-catalyzed hydroamination is initiated by activation of a C–C multiple bond followed by nucleophilic attack. Two types of initial coordination of a C–C multiple bond are conceivable; the direct η^2-coordination of a C–C multiple bond and the more extended π-coordination system such as a η^3-allyl system (or a η^6-arene system).

A symmetrically η^2-coordinated olefin is deactivated to nucleophilic attack; thus it should be noted that slippage and deformation to η^1-coordination plays a crucial role in activating for the nucleophilic addition (Eq. 2) [20, 30–32]. The theoretical studies predicted that in the slipped η^1-coordinated olefin, a lowest unoccupied molecular orbital (LUMO) is lowered in energy and localized on the β-carbon. The slipping to η^1-coordination enables the interaction with external nucleophile and the transition state would be η^1-like structure.



(2)

The direction of nucleophilic attack was proved to be *trans* (from *anti* side of metal) using platinum complex bearing a prochiral olefin. The diastereomerically pure alkene-complex **5** reacted with an amine **6**, to generate, after acid hydrolysis, (*S*)-amine salt **7** corresponding to *trans*-addition (Eq. 3) [33–35].



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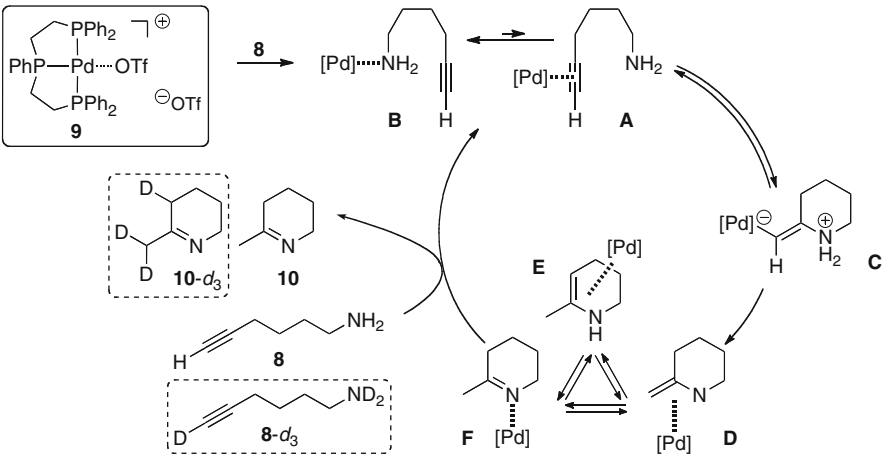
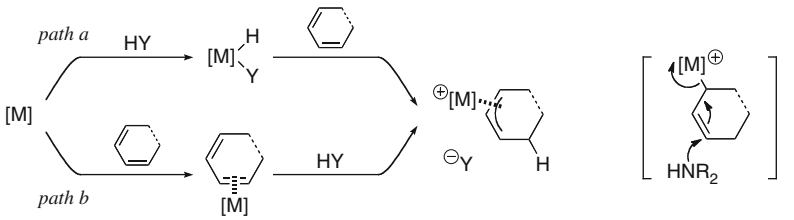


Scheme 3 An example of intramolecular hydroamination of aminoalkyne

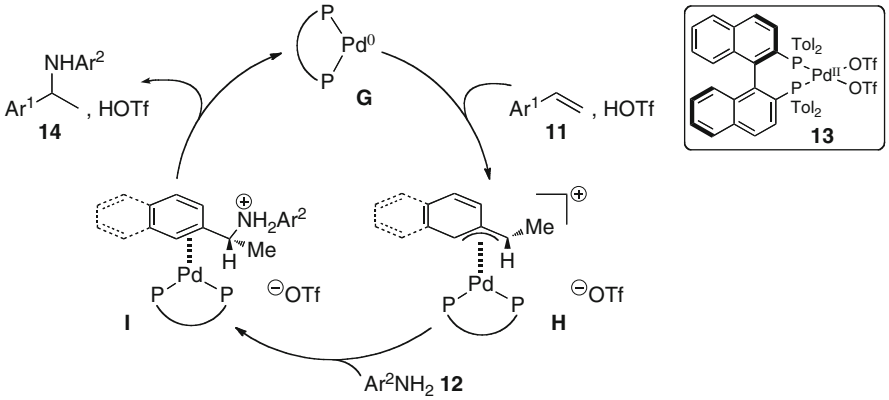
3.1.2 Nucleophilic Addition on Coordinated Alkenes or Alkynes

As a typical example, the intramolecular hydroamination of 6-aminohex-1-yne (**8**) catalyzed by [Pd(Triphos)](OTf)$_2$ (**9**) is shown in Scheme 3 [36]. By coordinating directly to a Lewis acidic metal center (**A**), the C–C multiple bond turns feasible for nucleophilic addition. After the nucleophilic addition to η^2-coordinated alkyne occurred, the M–C bond of metal-vinyl intermediate **C** was cleaved to afford hydroamination products. A remarkable enhancement of catalytic efficiency was achieved by addition of a Brønsted acid as cocatalyst [37].

As detailed below, the evidences of the catalytic processes were brought out by several methods utilizing rigorous systematic comparison of the mixtures of substrate (aminoalkyne **8**, 1-hexyne as an alkyne analogue, or 1-hexylamine as an amine analogue), palladium complex (**9** or its acetate analogue), and/or additive (acid or base). (1) By titration calorimetry and in situ IR spectroscopy, it is suggested that the initial interaction of **8** with palladium occurs at an amine moiety (**B**). (2) From the NMR analysis of various reaction combination, the predominant intermediate was fully assigned as **C**, which would be generated from the nucleophilic addition of coordinated alkyne **A**, indicating that the intermediate **A** would be brought about through the isomerization of **B** and that the M–C cleavage of **C** is rate limiting. (3) In the deuterium labeling experiment, all the deuteriums of **8**-d_3 in the above reaction were transferred to the product **10**-d_3, indicating that hydrogen shift occurs more likely in intramolecular way probably by palladium assistance through **D**, **E**, and **F** [22]. (4) When an additive acid exists, it would act as cocatalyst in the following two ways: (a) increase the coordination probability at alkyne moiety in **8** (**A**) by decreasing the coordination ability of the amine moiety which would be converted into ammonium salt, and (b) promote the protolytic cleavage of the M–C bond by utilizing intermolecular way, such as protonation of M–C bond or that of metal center [38–40].



Scheme 4 Two pathways for producing η^3-coordinated allyl metal species in hydroamination



Scheme 5 Hydroamination of vinylarene through η^3-benzyl palladium

3.1.3 Nucleophilic Addition to Other π-Coordination Systems

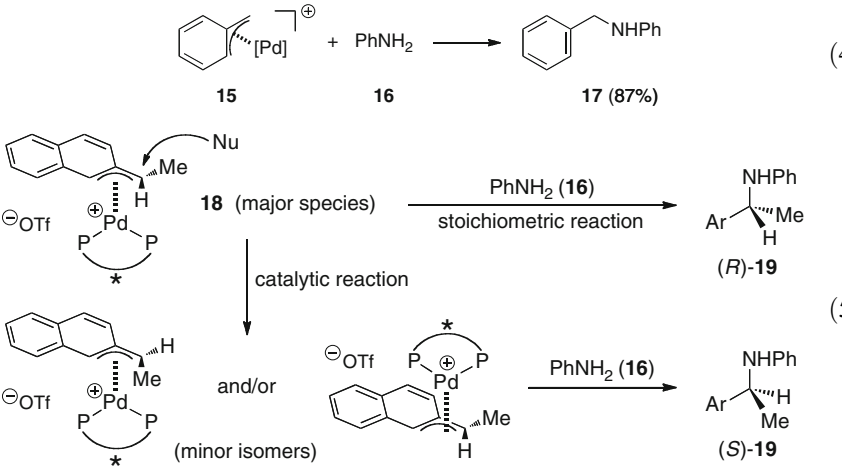
Intermediacy of η^3-Allyl System

In addition to η^2-coordinated alkenes or alkynes, the η^3-coordinated allyl metals undergo hydroamination. η^3-Allyl metal species of palladium and nickel are considered to be generated as major species during hydroamination of allenes, dienes, and trienes. Alkynes are also possible to produce η^3-allyl species via isomerization process. In the reaction of vinylarenes, η^3-benzyl metal species is generated as an intermediate.

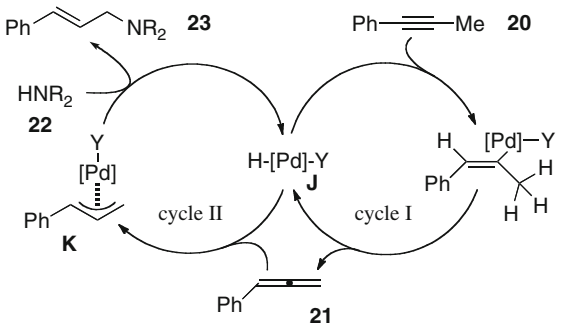
For producing η^3-coordinated allyl metal species, two pathways are proposed as shown in Scheme 4, and in either case an acid is involved, often added as a cocatalyst or in situ generated; *path (a)* formation of metal hydride species followed by coordination of C–C double bond and subsequent migratory insertion into M–H bond [hydrometallation], and *path* (*b*) coordination of C–C double bond followed by protonation of the coordinated alkene [41]. To the terminal carbon of the η^3-allyl system, an amine attacks from external side. This type of hydroamination has different characteristics in that the formation of C–H bond precedes by the formation of C–N bond, by contrast to the reactions of other mechanisms which have the opposite bond-forming order, that is, the formation of C–N bond occurs first.

As an interesting and informative example, the intermolecular hydroamination of vinylarene **11** with arylamine **12** in the presence of pre-catalyst [(*R*)-Tol-BINAP]Pd(OTf)$_2$ (**13**) is shown in Scheme 5 [41–46]. Although η^2-olefin complex formation appears possible, the isolated and crystallographically characterized species was *syn*-η^3-benzyl metal complex **H**. Complex **H** leads to the benzylic amine π-complex **I** through external nucleophilic attack of **12** directly to the benzylic carbon without pre-coordination to palladium. Finally hydroamination product **14** is extruded through the ligand exchange with vinylarene **11**.

As detailed below, some of the elementary processes involved in the catalysis were supported or substantiated experimentally. (1) An active catalyst appears to be Pd(0) species **G**, which can be derived by Wacker-type oxidation with the Pd (II) pre-catalyst **13**, and it is well supported by the detection of oxidized byproduct [41, 42]. (2) A *syn*-η^3-benzyl metal complex **H** (and **18**) was unambiguously determined. (3) In Eq. (4), treatment of a η^3-benzyl complex **15**, which cannot generate olefin, with aniline (**16**) furnishes a benzylamine derivative **17** in a high yield, and verifying nucleophilic attack of an amine to η^3-benzyl complexes is a facile process. (4) The steric course of the C–N bond-forming process in stoichiometric reaction of enantio- and diastereomerically pure **18** with amine **16** gave (*R*)-**19** predominantly, indicating that the nucleophilic attack occurs from external side (Eq. 5). *However, in the catalytic reaction, the configuration of predominant product was* (*S*)*, opposite to the stoichiometric reaction*. The detection of minor species other than **18** proposed that the reaction of the major species **18** with amine is slower than that of the minor isomers which lead to (*S*)-**19**. This sort of phenomena has been frequently observed in asymmetric hydrogenation [47].



Depending on the catalyst, alkynes can undergo hydroamination via prior isomerization to allene followed by generation of η^3-allyl intermediate (Scheme 6)



Scheme 6 Isomerization–hydroamination process of alkynes

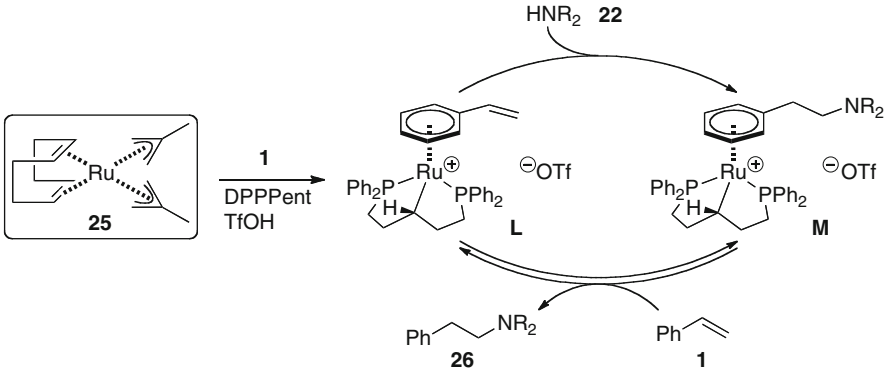
[48–50]. To a hydridopalladium species **J** generated from $Pd(PPh_3)_4$ and benzoic acid, hydropalladation of alkyne **20** and subsequent β-hydride elimination occur to give allene **21** and to regenerate the active catalyst **J** (cycle I). Subsequent hydropalladation of **21** with **J** affords the η^3-allyl palladium **K**, and external nucleophilic attack gives hydroamination product **23** (cycle II). Intramolecular version is also documented in Sect. 4.1.

Intermediacy of η^6-Arene System

A totally different approach for hydroamination of vinylarene is realized by intermediacy of η^6-arene metal complex, facilitating nucleophilic attack of amines at the vinyl linkage due to the electron-withdrawing effect of metal. This type of activation might be brought by the use of d^6 metals, such as Cr^0, Fe^{II}, and Ru^{II} which are relatively easy to form η^6-arene complexes [51].

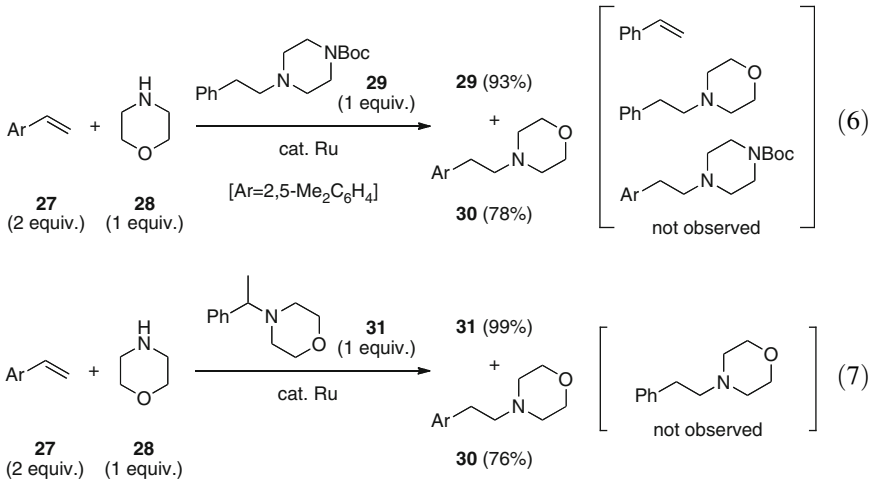
An intermolecular hydroamination of vinylarene **1** with alkylamine **22** was achieved by Ru(cod)(2-methylallyl)$_2$ (**25**) with DPPPent and TfOH (Scheme 7) [52, 53]. Two isolated and crystallographically characterized species were **L** and **M** of η^6-arene metal structure. The vinyl group in **L** is in approximately the same plane with the coordinated phenyl ring leading to the desirable conjugation for the activation by remotely positioned metal. The intermediate **M** has a structure just after the nucleophilic addition, also indicating the process of arene exchange to **L**.

The experiments illustrated in Eqs. (6) and (7) clearly indicate that the reaction proceeds in an irreversible and direct manner. (1) In Eq. (6), the coexistent hydroamination adduct **29** afforded neither free styrene nor crossover products, indicating that the hydroamination is an irreversible process. (2) In the reaction of 2,5-dimethylstyrene (**27**) with morphorine (**28**) in Eq. (7), an additive, Markovnikov-type adduct **31**, did not isomerize to anti-Markovnikov-type adduct. (3) The kinetic study on the amination process revealed a large negative $\Delta S^{\ddagger}$ of -213 J mol^{-1} s^{-1}, which is similar to the value of the nitroalkene amination. The first-order rate constant of the arene exchange process is comparable to that of the amination process. (4) The conjugate addition nature was confirmed by using



Scheme 7 Hydroamination pathway by η^6-arene ruthenium

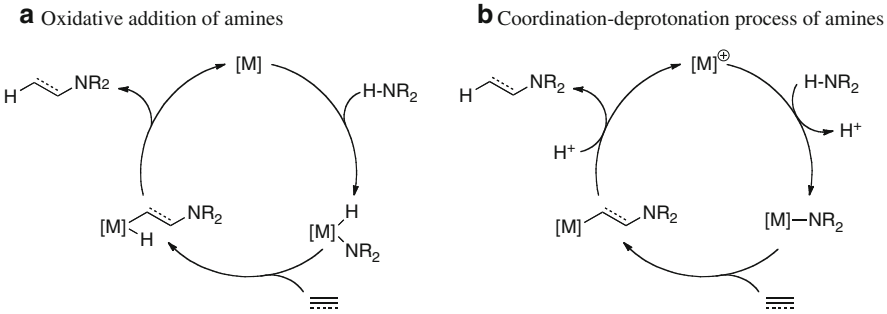
3,5-dimethoxyphenyl analogue of DPPPent as an electron-deficient catalyst to enhance the catalytic ability and the higher performance was observed. It is also likely to be associated with the larger steric demand, which is envisioned to facilitate the arene exchange process.



3.2 Amine Activation Pathway

3.2.1 Inner-Sphere Pathway

Activation of an amine by a coordinatively unsaturated late transition metal, which leads to metal amide species, is also proposed as a potential pathway (Scheme 8).



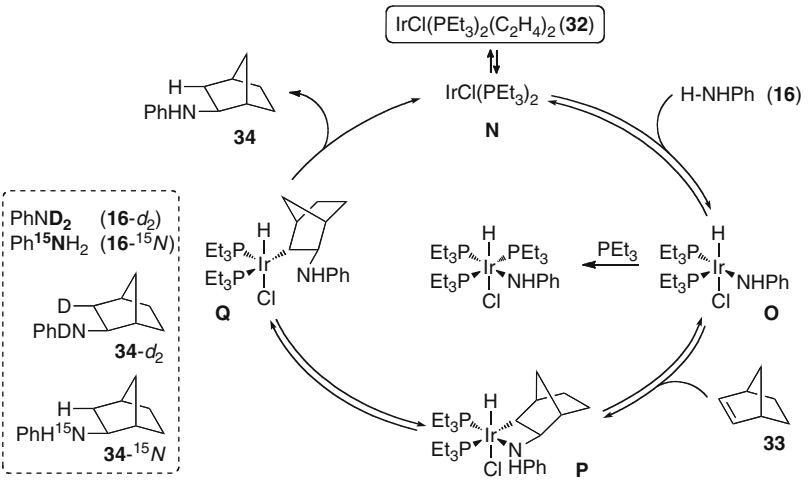
Scheme 8 Two pathways to generate metal amide species and successive hydroamination

Amine activation pathway has been well studied in catalysis by lanthanides, early transition metals, and alkali metals. In metal amide chemistry of late transition metals, there are mainly two pathways to synthesize metal amide complexes applicable under hydroamination conditions [54]. One is oxidative addition of amines to produce a metal amide species bearing hydride (Scheme 8a). The other gives a metal amide species by deprotonation of an amine metal intermediate derived from the coordination of amines to metal center, and it often occurs as ammonium salt elimination by the second amine molecule (Scheme 8b). Although the latter type of amido metal species is rather limited in hydroamination by late transition metals, it is often proposed in the mechanism of palladium-catalyzed oxidative amination reaction, which terminates the catalytic cycle by β-hydride elimination [26]. Hydroamination through aminometallation with metal amide species demands at least two coordination sites on metal, one for amine coordination and another for C–C multiple bond coordination. Accordingly, there is a marked difference between the hydroamination via C–C multiple bond activation, which demands one coordination site on metal, and via amine activation.

3.2.2 Aminometallation Initiated by Oxidative Addition of Amines

In this type of reaction, the oxidation number of the metal changes by ±2; therefore, this pathway works well through the redox couple of metals such as Pd^0/Pd^{II}, Pt^0/Pt^{II}, Rh^I/Rh^{III}, Ir^I/Ir^{III}, or Ru^0/Ru^{II}. For the reaction to occur, active catalysts should be compatible with all the changes of oxidation, coordination, and valence electron numbers.

An intermolecular hydroamination using pre-catalyst $IrCl(PEt_3)_2(C_2H_4)_2$ (**32**) has been elucidated as an overall *cis*-addition of the N–H bond across norbornene (**33**) (Scheme 9) [55]. The intermediate was crystallographically characterized as complex **P**, which was derived from migratory insertion of **33** into Ir–N bond of **O**, and both of its newly formed Ir–C and C–N bonds occupied the *exo*-face of **33**.



Scheme 9 Hydroamination of norbornene catalyzed by iridium

The isotope labeling experiments indicate that this reaction involves the elemental processes of oxidative addition and reductive elimination. (1) The reaction using *N,N*-d_2-aniline (**16**-d_2) afforded Ir-D analogue (**P**-d_2) as an intermediate, and finally the product **34**-d_2 was produced in which deuterium labeling took place exclusively at 3-*exo* position together with ND labeling. (2) The reaction using a mixture of singly labeled intermediates **P**-d_2 and **P**-^{15}N, **34**-d_2 and **34**-^{15}N proceeded quantitatively, though the crossover products such as non-labeled product **34** and doubly labeled product **34**-^{15}N-d_2 (in which two hydrogens of **34**-^{15}N were converted to two deuteriums) were not obtained. These results have proved that the N–H addition occurs oxidatively and the elimination of product reductively, not involving deprotonation and protonation processes. The efficiency of catalysis was improved using bisphosphine ligand with fluoride additive [56].

3.2.3 Aminometallation Initiated by Coordination of Amines

An alternative mechanism starts from the coordination of an amine, and the successive deprotonation gives a metal amide species (Scheme 8b). Coordination of a C–C multiple bond to this metal center is followed by migratory insertion into the M–N bond. The newly formed M–C bond is cleaved by protonolysis to regenerate the active metal species. The advantage of this pathway is that it does not require the change of oxidation number of metal, and it looks similar in mechanism to hydroamination of other group metals (for group 4 metals, metathetical reaction takes place at the step of C–N bond formation) and partially similar in mechanism to oxidative amination of late transition metals. However, so far, most hydroamination reactions catalyzed by late transition metals can be explained by the mechanisms discussed in Sects. 3.1 and 3.2.2. If the activation of the C–C

multiple bond is very difficult for some reasons and also the efficient redox cycle of metal is difficult, the reaction might proceed in this pathway.

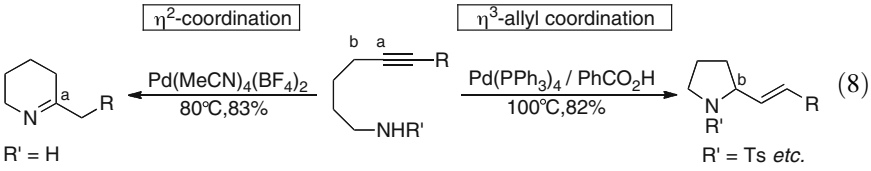
4 Scope of Late Transition Metal-Catalyzed Hydroamination

In the above sections, the mechanisms of the late transition metal-catalyzed hydroamination have been discussed mainly. In this section, the scope of the reaction is summarized concisely with selected examples. Due to space limitation, not all the examples are covered and the detailed reaction sequences/processes are not shown, but the catalysts used in the reactions are shown attached with reference number (the "*" attached references report enantio-/diastereo-selective or chirality transfer reactions). We hope that readers may understand what types of catalysts are used in the hydroamination, in addition to what type of molecular transformation is feasible in the hydroamination.

4.1 The Reaction Pathway Depending on Catalyst Species

As shown in Eq. (8), the reaction is able to proceed through either η^2-coordination or η^3-coordination pathway, and it depends on the catalyst species used in the reaction. In the reaction directed to left, η^2-coordination of alkyne followed by nucleophilic attack to carbon-*a* occurs [22, 23]. On the other hand, in the reaction directed to right, alkyne isomerization to allene takes place first, followed by η^3-allyl coordination, and subsequent nucleophilic attack to carbon-*b* (the terminal carbon of η^3-allyl metal species) takes place [48].

In the hydroamination of aminoallene, the product of Eq. (9) is comparable to that of Eq. (8) through η^3-allyl coordination. It should be noted that the reaction of chiral aminoallenes gives racemic products in the case of η^3-allyl metal system [49]; however, high chirality transfer occurs in the case of η^2-coordination system [57].



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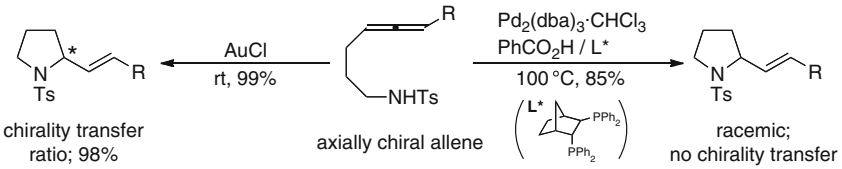
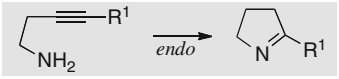


(9)

4.2 *Intramolecular Hydroamination of Alkynes*

The cyclization reactions of aminoalkynes proceed in *endo*- or *exo*- manner, and the reactions are catalyzed by various kinds of metal complexes as shown below. When the substrates of primary amine are used, the hydroamination products often isomerize to cyclic imines. Most reactions afford 5- or 6-membered ring products.

- 5-*endo* cyclizations and the catalysts; Eqs. (10) and (11)



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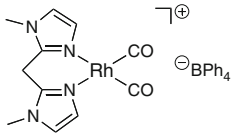
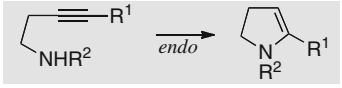


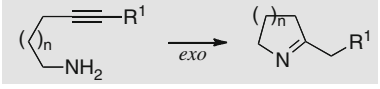
[58]



(11)

Et_2Zn [59]

- 5- or 6-*exo* cyclizations and the catalysts; Eqs. (12)–(15)



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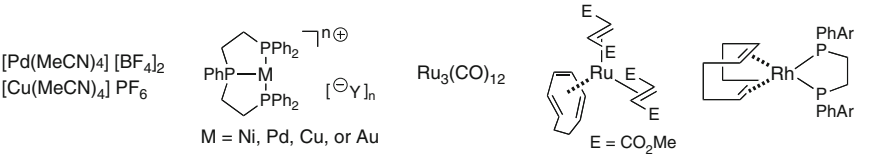
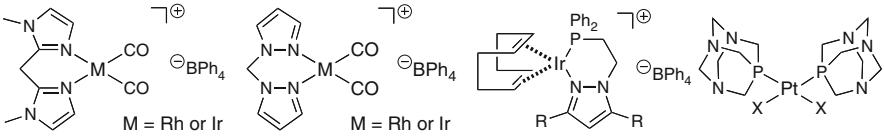


[21-23] [22, 23] [60] [60] [21, 22]



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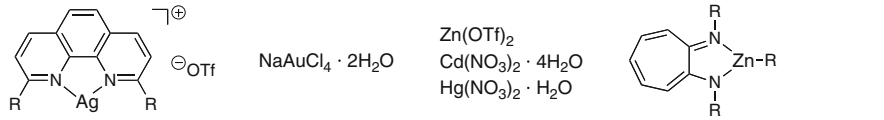
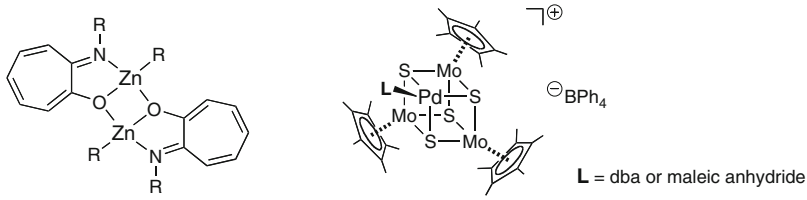
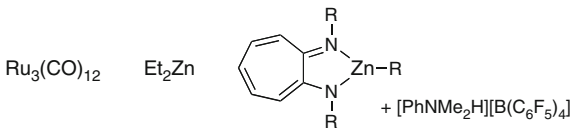


[63] [64] [22, 23] [65]

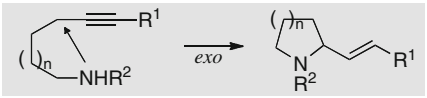


[65] [66]

(13)



[60] [59] [67]



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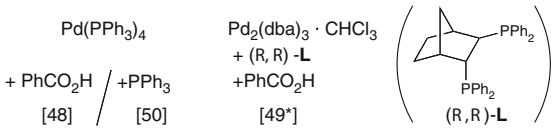

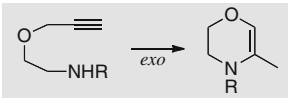

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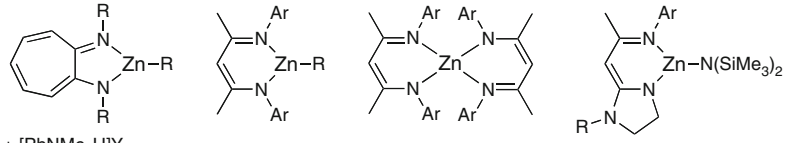
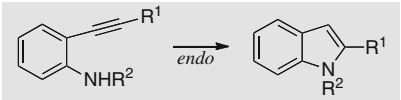
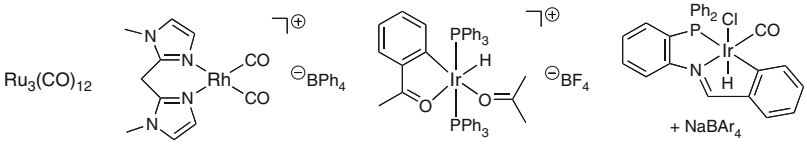


- 5- or 6-*endo* cyclizations of aminoalkynes bearing *o*-alkynylbenzene structure and the catalysts; Eqs. (16) and (17)

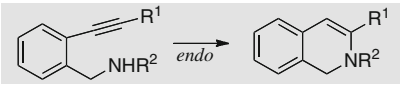


(16)



[60] [69] [70] [71]

$PdCl_2$	$PtCl_2$ (under CO)	$Cu(OAc)_2$	$NaAuCl_4 \cdot 2H_2O$	$NaAuCl_4 \cdot 2H_2O$ (in ionic liquid)	$ZnEt_2$
[72]	[73]	[74]	[72, 75]	[76]	[59]



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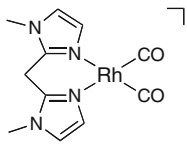
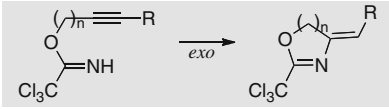


[69]	$PdPhCH_2Cl(PPh_3)_2 + Et_3N$	AgOTf	$ClAuPPh_3 + AgNTf_2$
	[77]	[78]	[79]

- 5- or 6-*exo* cyclizations of imidates and the catalysts; Eq. (18)



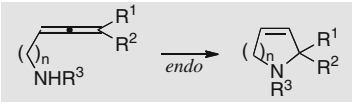
(18)

$AuCl_3$	$ClAuP(C_6F_5)_3 + AgSbF_6$	$ClAuPPh_3 + AgBF_4$
[80]	[81]	[81]

4.3 *Intramolecular Hydroamination of Allenes and Conjugated Dienes*

The cyclization reactions of aminoallenes proceed also in *endo*- or *exo*-manner. In the case of hydroamination of dienes, there are only limited examples.

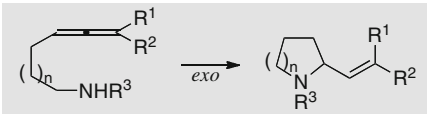
- 5- or 6-*endo* cyclizations of aminoallenes and the catalysts; Eq. (19)



(19)

$Ru_3(CO)_{12}$ + Et_3N [82] | $Cu(OTf)_2$ [83] | $AgNO_3$ [82] | $AuCl_3$ [84*] | AuCl [84*] | AuCl + pyridine [85]

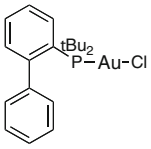
- 5- or 6-*exo* cyclizations of aminoallenes and the catalysts; Eq. (20)



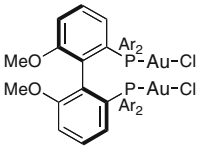
(20)

(1) η^2-coordination mechanism:
Chirality of allenes, ligands, and even anions can be well recognized.

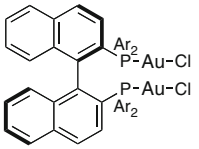
$AgNO_3$ | $AgBF_4$ | $AuCl_3$, $AuBr_3$, AuCl [57*, 88]



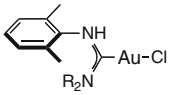
+ AgOTf [89*]



+ $AgClO_4$ [90* , 91*]

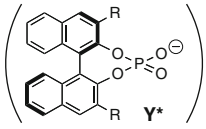


+ AgY (Y = p-nitrobenzoate) [92*, 93*]

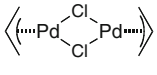


+ AgOTs [94]

$ClAuPR_3$ + AgY* [95*]

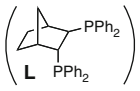


(2) η^3-allyl coordination mechanism

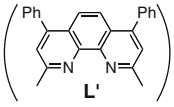


+ dppf + AcOH [96]

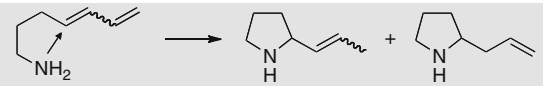
$Pd_2(dba)_3 \cdot CHCl_3$ + **L** + $PhCO_2H$ [49]



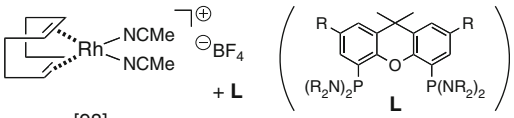
$PdCl_2$ + **L'** + NaOAc + MA (MA = maleicanhydride) [97]



- Cyclizations of aminodienes and the catalysts; Eqs. (21)–(23) (see also Sect. 3.1.3.1)
The nucleophile addition occurs at either terminal or internal carbon of dienes.

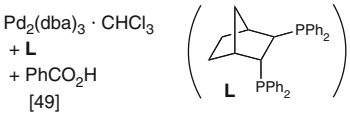


(21)

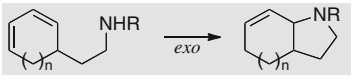


[98]

(22)



[49]



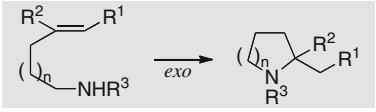
(23)

$ClAuPPh_3$ + AgOTf [99]

4.4 *Intramolecular Hydroamination of Alkenes*

The cyclization reactions of aminoalkenes proceed in *exo*- or *endo*-manner. Generally, higher reaction temperatures with increased catalyst loading and longer reaction times are needed in the reactions of aminoalkenes, compared to those of aminoalkynes or aminoallenes.

- 5- or 6-exo cyclizations and the catalysts; Eq. (24)



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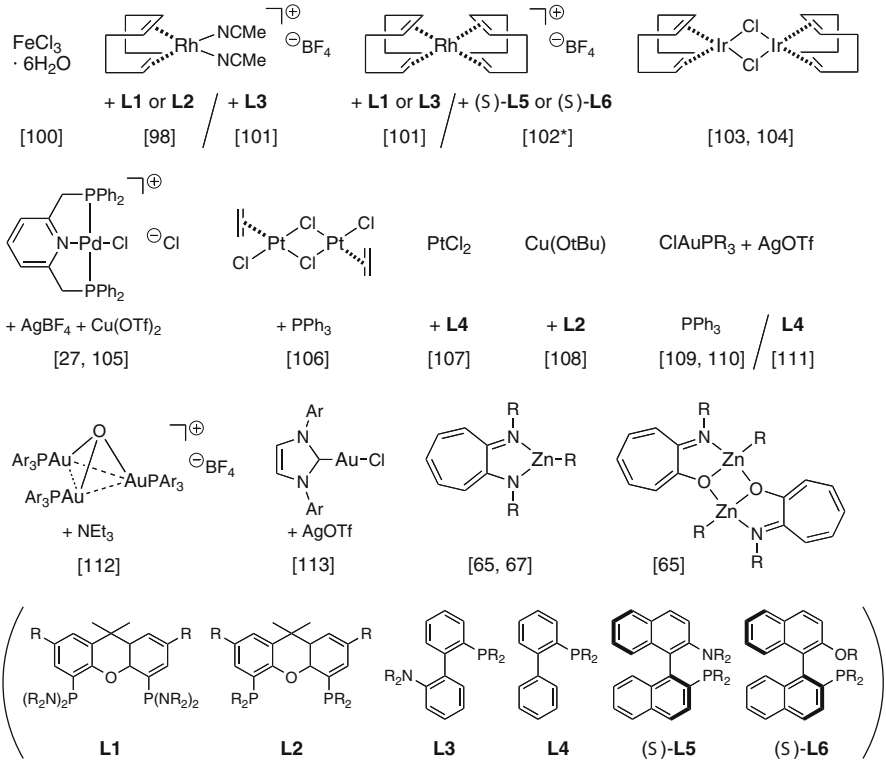
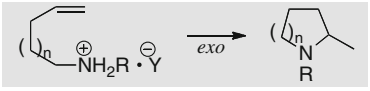


- Cyclization of ammonium salts; Eq. (25)



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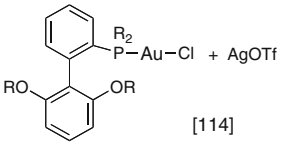
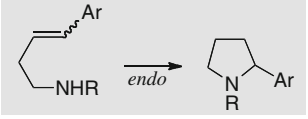


- 5- or 6-*endo* cyclization and the catalysts; Eqs. (26) and (27)



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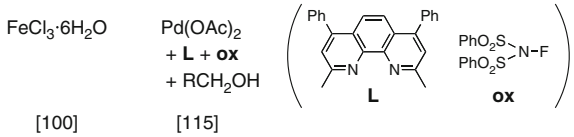
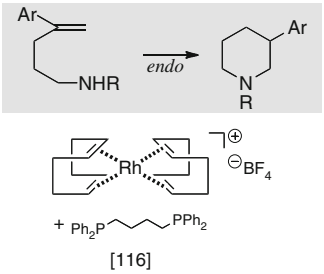




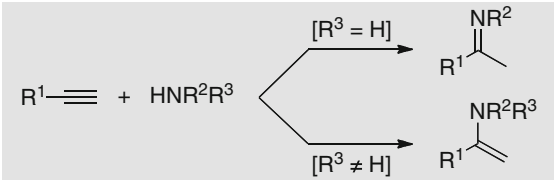
(27)

[116]

4.5 *Intermolecular Hydroamination*

The intermolecular hydroamination reactions of alkynes and alkenes occur with Markovnikov or *anti*-Markovnikov selectivity. The nucleophilic addition to allenes occurs at terminal carbon of allenes not at central one.

- Markovnikov addition to alkynes and the catalysts; Eq. (28)



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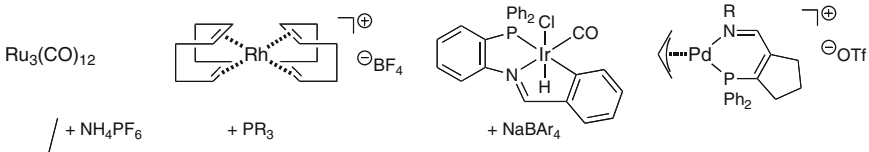
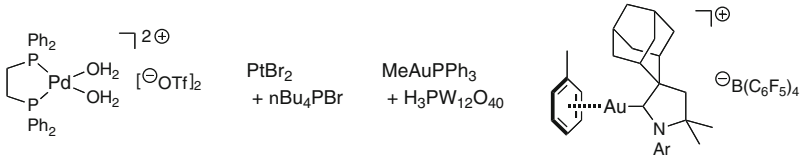
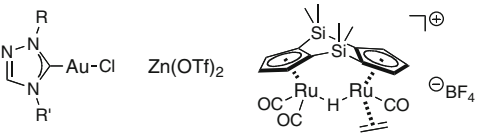


[117] [118] [119] [71] [120]

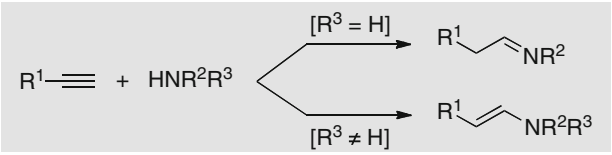


[121] [122] [123] [124]

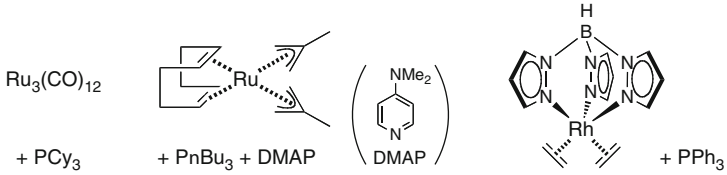


[125] [126] [127]

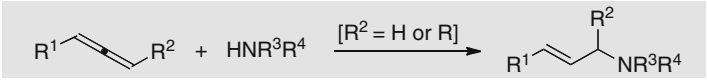
- *Anti*-Markovnikov addition to alkynes and the catalysts; Eq. (29)
  Catalysts [128] and [129] gave *Z*-enamines as a minor product.
  A vinylidene rhodium intermediate was supposed in the reaction of catalyst [130].



(29)



- Nucleophilic addition to terminal carbon of allenes and the catalysts; Eqs. (30) and (31)
  The nucleophilic attack occurs often at less substituted terminal carbon like in Eq. (30); however, the hindered terminal carbon can be attacked as shown in Eq. (31).



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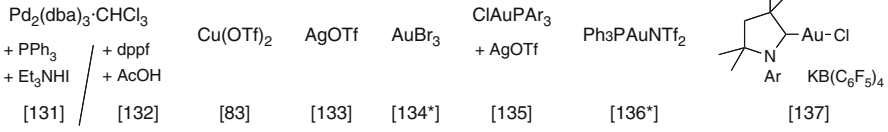
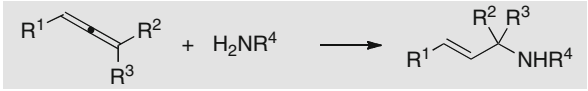
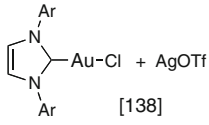
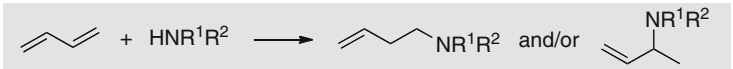




(31)



- Nucleophilic addition to terminal or internal carbon of dienes and the catalysts; Eq. (32) (see also Sect. 3.1.3.1)



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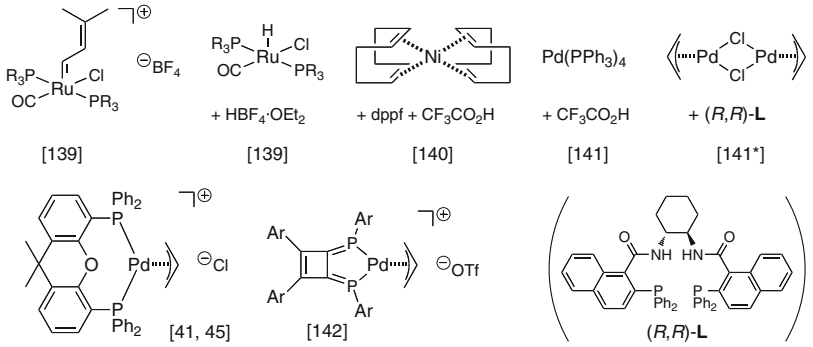
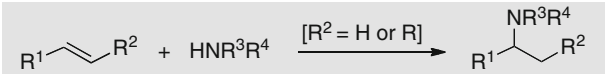
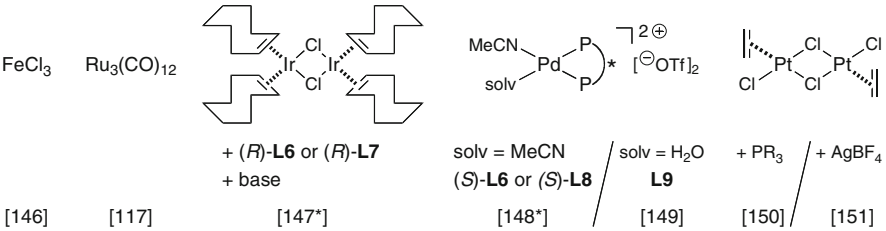
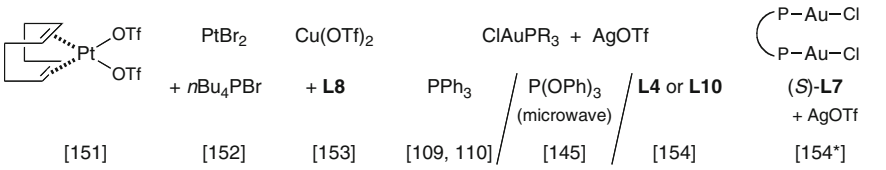


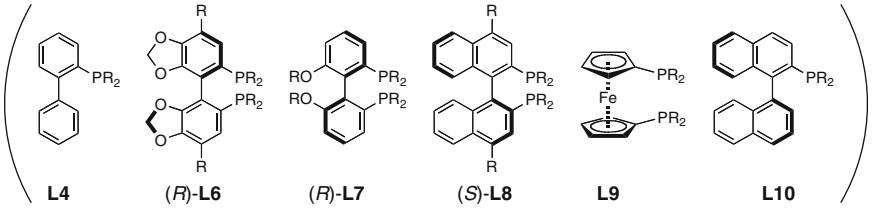
- Markovnikov additions of alkenes and the catalysts; Eq. (33)



(33)

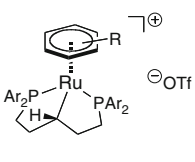




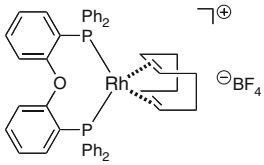


- *Anti*-Markovnikov additions of alkenes and the catalysts; Eq. (34)

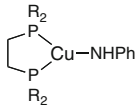
(34)



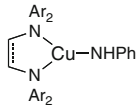
[52, 53]



[155]



[156]



[156]

5 Conclusion

This chapter summarizes the late transition metal-catalyzed hydroamination focusing on the mechanistic discussion and on the catalyst species. A great number of metal complexes have been designed and they exhibit excellent catalytic properties. Significant progress has been made in this research field; however, there still remain difficult problems which should be overcome from synthetic point of view. For example, the intermolecular reactions of simple alkenes and alkyl amines are not able to proceed nicely. Further mechanistic studies and deep understandings for reaction pathways and catalytic systems may solve such remaining problems.

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Chiral Metal Complex-Promoted Asymmetric Hydrophosphinations

Sumod A. Pullarkat and Pak-Hing Leung

Abstract This chapter provides an account of the synthesis of a series of chiral tertiary phosphines via the metal complex-assisted asymmetric hydrophosphination methodology which involves secondary phosphines as the nucleophiles. Chiral aza- and phosphapalladacycles are found to function as highly efficient templates or catalysts for the asymmetric P–H addition reaction. The versatile protocol allows for the asymmetric hydrophosphination of olefinic C=C bonds of monophosphines thus yielding a family of tertiary C*-diphosphines as well as C*P*-diphosphines, depending on the nucleophile employed. The addition of two equivalents of $HPPh_2$ to symmetrical bifunctionalized alkynes leading to generation of two new C* centers is also supported. The air-sensitive nucleophiles and the unsaturated substrates containing unprotected functionalities such as aldehyde, keto, ester, cyano, and alcohol can be utilized directly under this mild and facile reaction conditions. The methodology is equally efficient when applied to the generation of P–N ligand systems via hydrophosphination of unsaturated pyridyl-based substrates as well as systems with C=N moieties. The protocol has also the added advantage of allowing the selective formation of 1,1-, 1,2-, and 1,3-diphosphines simply by judicious control of reaction conditions. This reaction can also be extended to the synthesis of chiral triphosphine systems. This synthetic strategy therefore promises to be a versatile approach for the generation of a wide range of chiral tertiary phosphine ligands with potential applications in catalysis.

Keywords Asymmetric hydrophosphination · Palladacycle · P–H addition · Phosphine

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1 Introduction

Over the past few decades, enantiomerically pure tertiary phosphines have attracted considerable interest by virtue of the fact that they have proven themselves as important ligands in asymmetric synthesis and catalysis [1–4].In spite of the continuing interest in the development of analogous ligand systems such as those involving carbenes, chiral phosphines have maintained their role as the most frequently employed class of ligand auxiliaries in transition metal-catalyzed asymmetric reactions. One of the most important type of phosphine ligands in this field has been diphosphines bearing C-, P-, or both P- and C-stereogenic centers as well as those incorporating planar chirality [5].

In the field of organophosphorous chemistry dealing specifically with the synthesis of new phosphine moieties, the addition of P–H bonds to unsaturated substrates assumes enormous significance in terms of synthetic value as well as atom economy. However, due to the lack of a natural chiral pool and the inherent configurational instability of phosphorous stereocenters (especially at the elevated temperatures often required in their synthetic protocols), the direct synthesis of tertiary chiral diphosphines containing P- and C-stereogenic centers has posed considerable challenges to scientists working in the field. Asymmetric hydrophosphinations have therefore become a potentially effective, albeit enormously challenging, synthetic strategy for the preparation of chiral phosphines for potential applications in asymmetric synthesis and biological studies. Such additions to unsaturated carbon–carbon moieties can typically proceed via thermal [6–8], acidic [9, 10],basic [11–13], or free radical [14–18] pathways leading to the formation of a wide variety of phosphines including a wide array of diphosphine substrates.

Chiral metallacycles have been employed as auxiliaries for the promotion and control of asymmetric reactions such as Diels–Alder cycloadditions involving phospholes [19]. This synthetic methodology can be extended to the synthesis of diphosphine motifs via asymmetric hydrophosphination of vinylic and other unsaturated phosphine-functionalized substrates. The advantages offered by these metal complexes are listed below:

1. They are robust in a wide range of reaction conditions used for hydrophosphinations including the presence of bases.
2. They are easy to prepare in large scale and typically takes about a week's time in synthesis and purification.

3. The stereochemistry and electronic properties exerted by these complexes in scenarios such as Diels–Alder reactions have proved beyond doubt that they are efficient at controlling the stereochemistry of chiral centers formed via the intramolecular (*exo* cycloadditions) as well as intermolecular (*endo* cycloadditions) pathways, in predictable manners [19].
4. When used in hydrophosphination reactions where air-sensitive secondary phosphines are employed, they afford simultaneous protection and assistance in deprotonation of these species by coordination and subsequent activation of the P–H bond, thus priming them for the subsequent attack on C=C centers.
5. These complexes in most cases also provide the avenue for isolation via fractional crystallization or column chromatography of the diastereomeric chiral diphosphines and their comprehensive characterization while coordinated to the metal center using ^{1}H (^{1}D and ^{2}D ROESY), ^{13}C, and ^{31}P NMR as well as by single-crystal X-ray diffraction.
6. The coordinated diphosphines are quite robust and can be stored for a long period of time in air, and they provide easy access to the free chiral phosphine ligands via a simple liberation procedure. This also allows the synthesis of various transition metal derivatives for purposes such as catalyst screening.

The aim of this chapter is to review the work conducted on the asymmetric P–H addition reactions involving secondary phosphines controlled, promoted, and catalyzed by palladacycles. A recent comprehensive review covering P–H additions has been published by Glueck et al., and this review will not replicate topics discussed in that work [20]. Other aspects of P–H additions such as those involving addition of phosphine adducts or phosphine oxides are dealt with in a separate chapter of this volume [21]. The chapter has been categorized based on the kind of substrates on which the P–H addition was undertaken.

2 Asymmetric Hydrophosphination of 1-Alken-1-ylphosphines

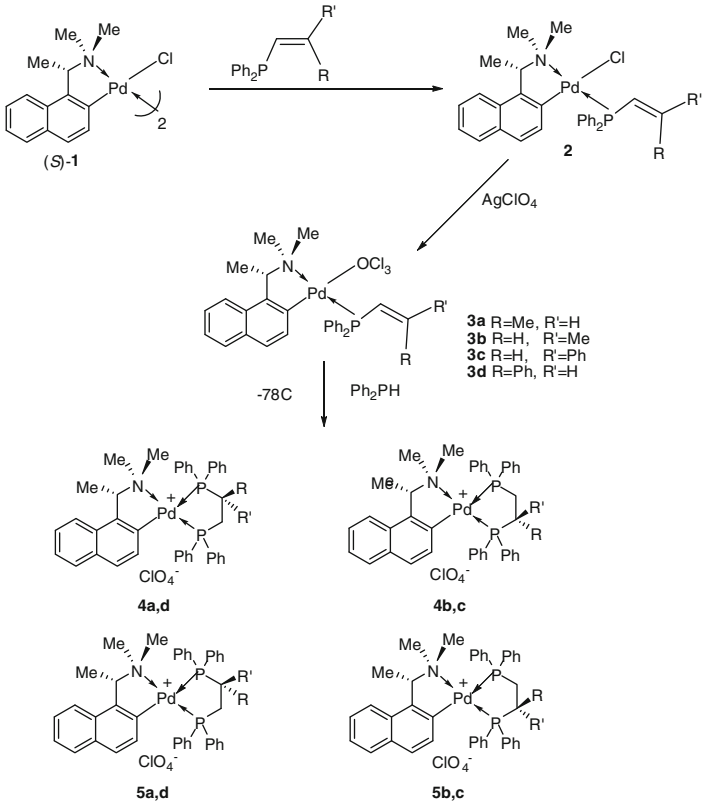
Since the pioneering work by Knowles, Sabacky, Horner, and coworkers in the late 1960s [22, 23], the development of optically pure P-chiral phosphorous ligands with the aim of incorporating them as auxiliaries for the design of chiral metal catalysts has attracted significant attention. The fact that the very first P-chiral diphosphine, DIPAMP, proved to be a very efficient motif in the design of metal catalysts for hydrogenation reactions further fuelled this interest [24]. On the other hand, diphosphines with chiral carbon center(s) in their backbones, such as DIOP and ChiraPhos, are another class of phosphine ligands that have shown their potential in asymmetric catalysis [25–27]. In this context, the asymmetric addition of a P–H moiety across the C–C double bond of an unsaturated compound such as an alkene is one of the most straightforward reactions that can produce such compounds.

In terms of understanding the mechanistic aspects involved in such additions on vinylic substrates via organometallic catalysts, analogies have been drawn to the hydroamination reactions [28–30]. Chiral metal complex-promoted asymmetric hydroaminations have been proposed to follow two different pathways. The first involves a sequence that commences with the oxidative addition of the N–H bond onto the metal ion followed by the insertion of the olefin and subsequent reductive elimination of the chiral substrate. An alternative pathway has also been proposed which involves the nucleophilic attack by the free amine on a coordinated olefin and a final protonolysis sequence, which leads to the release of the final product. Similar studies on metal ion-induced hydrophosphinations have been reported, and the mechanisms suspected to be in play include those proposed by Glueck and coworkers which basically involves the oxidative addition of a secondary phosphine followed by an olefin insertion [31]. Togni and coworkers have also observed in certain scenarios the coordination of the olefin to the catalyst metal center followed by the addition of a secondary phosphine across the C–C double bond [32].

Chiral cyclometallated complexes have proven to be effective in asymmetric C–C bond forming reactions, and this body of work has been reviewed previously [19] with extensive amount of data added subsequently [33–38]. In view of the efficacy of that methodology in the activation and subsequent stereocontrolled C–C bond formation reaction (of what in most cases were essentially two phosphine moieties), it seemed logical to explore the possibility of using a similar protocol for P–C bond formations.

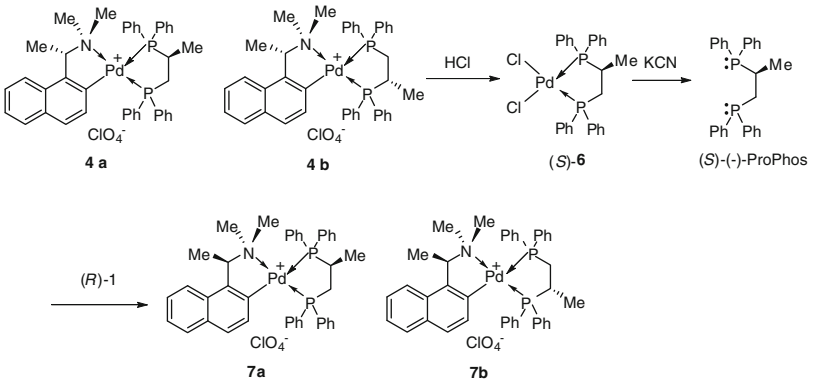
Diphosphine ligands such as 1,2-bis(diphenylphosphino)propane (ProPhos) and 1-phenyl-1,2-bis(diphenylphosphino)ethane (PhenPhos) have been traditionally prepared from naturally occurring chirons via tedious manipulations. PhenPhos, for instance, was first synthesized from chiral mandelic acid via a 3-step transformation [39, 40]. These two diphosphines are good illustrations for the efficacy of the chiral palladacycle-based methodology for the synthesis of C-chiral diphosphines in their enantiomerically pure form. The general synthetic protocol adopted for the synthesis of ProPhos and PhenPhos is shown in Scheme 1. One of the very first reactions on which the methodology was tested was the hydrophosphination of diphenyl-1-propenylphosphine [41]. It needs to be noted in this context that under ambient conditions, both (*E*)- and (*Z*)-diphenyl-1-propenylphoshines do not exhibit any reactivity toward typical hydrophosphinating agents such as diphenylphosphine when treated directly in the absence of a metal ion. The vinylphosphines were therefore coordinated to the chiral auxiliary (*S*)-**1** thus selectively generating the monophosphine palladium complex **2**. The kinetically inert Cl ligand *trans* to the C of the cyclopalladated ring was subsequently replaced by a labile moiety such as perchlorate in order to allow simultaneous coordination of both phosphine moieties on the metal center.

Subsequent addition of diphenylphosphine to the solution under nitrogen at −78°C led to the generation of the hydrophosphination products in 16 h as evident from the $^{31}P\{^{1}H\}$ NMR spectrum of the crude reaction mixture. The *cis-trans* regioisomeric pairs **4a**,**b** and **5a**,**b** are the four possible stereoisomeric products of



Scheme 1 Metal complex promoted asymmetric synthesis of ProPhos and PhenPhos

the hydrophosphination reactions. Regioisomers **4a**,**b** have the same *S* abolute configuration at the newly generated chiral carbon whereas **5a**,**b** have the *R* absolute configuration on the C-chiral center. For the reaction involving (*Z*)-diphenyl-1-propenylphosphine bearing Pd complex **3a**, the ^{31}P NMR spectrum in $CDCl_3$ exhibited three pairs of doublets in the ratio of 8:3:1. However, when monitored over several days, it was found to form an equilibrium mixture in which a fourth stereoisomeric product was also detected as a minor component with a new product ratio to 25:25:4:1. This is attributed to the steady state attainment in a *cis-trans* isomerization process which has been known to occur in similar diphoshine chelates with retention of absolute configuration [42]. It is noteworthy that the ratio of the two major products had changed from 8:3 to 1:1. Subsequent isolation of the major isomers via fractional crystallization in 64% yield led to their identification by single-crystal X-ray diffraction analysis, as regioisomers **4a**,**b**. Further treatment of the regioisomers with hydrochloric acid led to the chemoselective removal of the naphthylamine auxiliary yielding the optically pure neutral dichloro palladium complex (*S*)-**6** in 92% yield (Scheme 2).



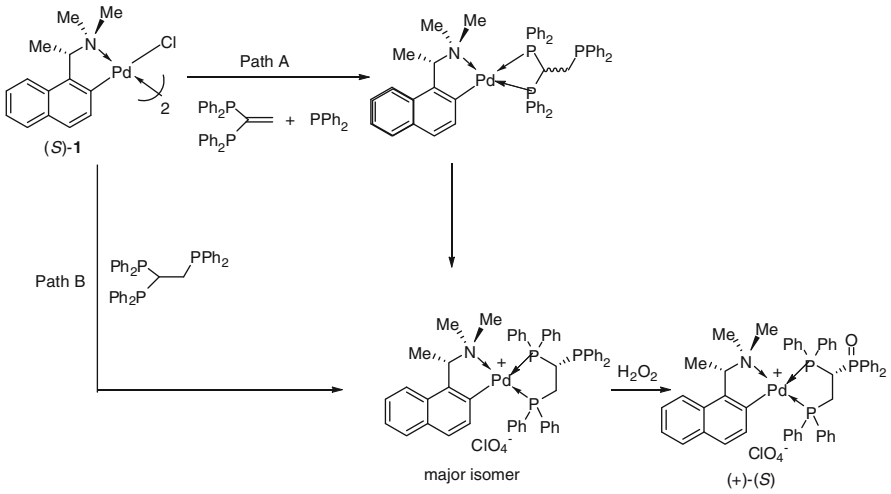
Scheme 2 Procedure adopted for the liberation of optically pure ProPhos and the confirmation of optical purity via recoordination

Treatment of the dichloro complex with aqueous cyanide under mild reaction conditions led to the isolation of the optically pure (*S*)-(−)-ProPhos in 95% yield in 2 h. This protocol also allows the opportunity to confirm whether the isolated free phosphine's optical purity has been compromised during the liberation process. This is a standard protocol which is used in all subsequent reactions discussed in this chapter. As seen in Scheme 2, **7a** and **7b** are the enantiomers of complexes **5a** and **5b** and, therefore, in the absence of any chiral shift reagent, they exhibit exactly the same chemical shifts. It is important to note that enantiomer (*R*)-(+)-ProPhos can also be prepared in a similar efficient manner by using the equally accessible complex (*R*)-**1** as the chiral auxiliary.

In order to get a better understanding of the manner in which the stereochemical control is exerted during the course of this reaction, we studied a similar reaction involving the (*E*)-isomer **3b** and found that the predominant products were **5a** and **5b** with *R* absolute configuration at the chiral carbon center. It was also found during the course of this study that strong bases led to the erosion of stereoselectivity possibly due to a hydrogen abstraction process.

A similar protocol as detailed above was also later used in the asymmetric synthesis of PhenPhos using the same chiral auxiliary [43]. For the reaction of **3c** with diphenylphosphine (Scheme 1), three products were formed in the ratio 12:2:1 and, for **3d,** two were formed in the ratio 6:1 with **4d** and **5d** being the major products (21% yield) and only trace amounts of **4c** and **5c** being formed. The optically pure **4d** was subsequently isolated by fractional crystallization.

The synthetic methodology is not limited to diphosphines and could easily be extended to the asymmetric synthesis of triphosphine ligands such as 1,1,2-tris (diphenylphosphino)ethane (Scheme 3) [44]. Although the free triphosphine itself is not chiral in this instance, a chiral center is generated once it is chelated to a metal. Nucleophilic addition of diphenylphosphine to the metal template activated 1,1-bis(diphenylphosphino)ethane proceeds smoothly to give a (solvent independent) equilibrium mixture of four diastereomeric products in an equilibrium ratio of



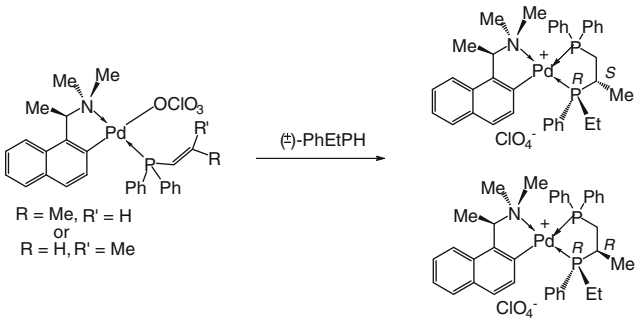
Scheme 3 Synthesis of 1,1,2-tris(diphenylphosphino)ethane

17:5:2:3. The nucleophilic addition is believed to proceed through a sterically unfavorable and kinetically labile four-membered chelate complex which subsequently rearranges to the less-strained five-membered products. In order to confirm this, the preformed triphosphine ligand was directly used (Path B, Scheme 3), and it led to the formation of the five-membered chelate in the same equilibrium ratio.

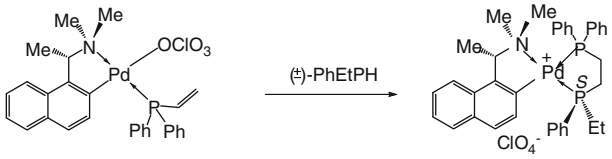
Subsequent to the attainment of equilibrium (via either Path A or B) over a period of one day, a stereoselective oxidation of the complex was attempted using aqueous hydrogen peroxide (30%) with the aim of obtaining a chiral mixed phopshine–phosphine oxide ligand. The monooxidation products were obtained in the ratio of 14:3:3:1. Subsequent to removal of the chiral auxiliary, the major isomer was crystallized out in 40% yield and comprehensively characterized.

The efficacy of the chiral auxiliary is not limited to the generation of the C-chiral centers in these systems and can very well be extended to simultaneous generation of both P- and C-chiral centers during the asymmetric hydrophosphination. The asymmetric hydrophosphination of (*E*)/(*Z*)-diphenyl-1-propenylphosphine using the racemic secondary phosphine (±)-PhEtPH and employing the same chiral auxiliary (*R*)-**1** has also been studied [45]. It needs to be noted that since the hydrophosphination agent itself in this instance is a racemic secondary phosphine with an unstable configuration. The coordination of (±)-PhEtPH to the metal center can therefore generate two different stereocenters on the phosphorous, thus generating up to eight stereoisomeric products in the absence of chiral control.

This is indeed a very challenging scenario in phosphine chemistry. However, the reaction of (*E*)-diphenyl-1-propenylphosphine with (±)-PhEtPH showed excellent selectivity with only four products formed in the ratio 9:5:1:1 (9:5 being subsequently confirmed as the regioisomeric ratio) with the major product being isolated via fractional crystallization in 60% yield (Scheme 4). The high yield is due to the crystallization-induced asymmetric disequilibration [46]. A similar reaction carried out with (*Z*)-diphenyl-1-propenylphosphine formed four stereoisomeric products in



Scheme 4 Asymmetric hydrophosphination of diphenyl-1-propenylphosphine using PhEtPH

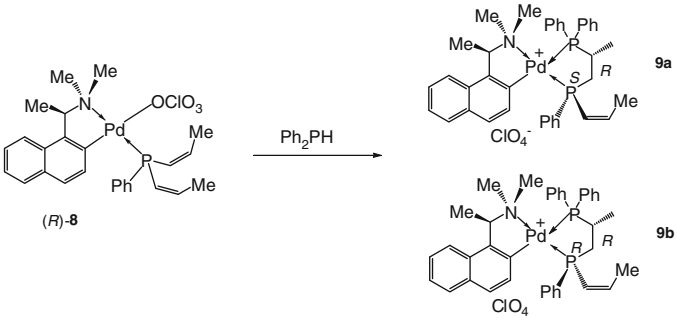


Scheme 5 Asymmetric hydrophosphination of diphenylvinylphosphine using PhEtPH

the ratio 24:13:2:1. The major product in this instance was isolated in 40% yield. In order to understand the chiral directing influence better, a hydrophosphination reaction involving (±)-PhEtPH and diphenylvinylphosphine was carried out using (*S*)-**1**. The reaction yielded the two possible diastereomeric complexes in the ratio 14:1. A chromatographic separation of the diastereomeric mixture gave the major product in 20% yield (Scheme 5).

The ability of the chiral auxiliary for simultaneous control of P and C chirality was also seen in the asymmetric hydrophosphination of phenyldi[(*Z*)-prop-1-enyl]phosphine with high regio- and stereoselectivity under mild conditions (Scheme 6) [47].

The hydrophosphination reaction generated only two diastereomers in the ratio of 1:1. Both **9a** and **9b** adopt the same absolute configuration at the C-chiral center. The reaction exhibited high regioselectivity with the diphenylphosphino group being added exclusively to the β-carbon of the phenyldi[(*Z*)-prop-1-enyl]phosphine to form five-membered rings exclusively. It is noteworthy in this instance that only one of the two 1-propen-1-yl groups in (*R*)-**8** reacted with diphenylphosphine. In contrast to the reaction involving 1,1-bis(diphenylphosphino)ethene, the dangling vinyl group in diastereomeric complexes **9a** and **9b** did not react further with excess diphenylphosphine to form the triphosphine. This is further indication that the hydrophosphination reaction requires both the secondary phosphine and the substrate to be coordinated simultaneously onto the palladium template during the course of the addition reaction. The kinetic stability of the five-membered diphosphine chelate and the sterically congested environment around palladium deter the excess secondary phosphine from approaching the palladium center. This results in excellent regioselectivity in instances where multiple centers of unsaturation are present for a nucleophilic attack.

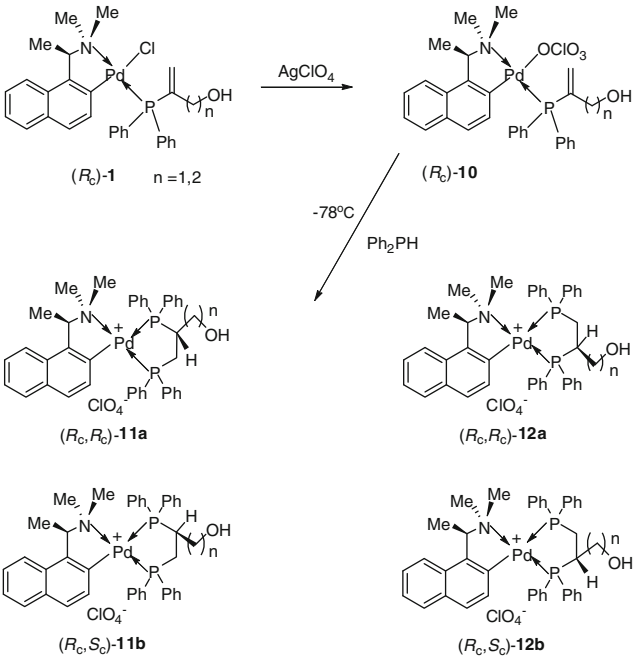


Scheme 6 Stereo- and regio-selective hydrophosphination of phenyldi[(Z)-prop-1enyl]phosphine

3 Asymmetric Hydrophosphination of Functionalized Phosphines

It is conceivable that the presence of selected functionalities on diphosphine skeletons can have an impact on both reactivity and enantioselectivity when employed in catalysis and also on their biological activity when used in fields such as chemotherapy [48–53]. Addition of P–H bonds to functionalized substrates with C–C multiple bonds continue to pose considerable challenges in view of the potential effects on the integrity of the functional group (especially in protocols that require thermal activation, strong bases, Brønsted acids, or radical initiators). The unique electronic and steric factor brought into play by these functionalities during the hydrophosphination process also needs to be taken into account. In view of the abovementioned factors, metal complexes offer superior reactivity, regioselectivity, and stereocontrol in hydrophosphination reactions in comparison with other reaction promoters such as strong bases, acids, and free radicals. The mild conditions required also means that many functional groups can be tolerated on substrates without any elaborate protection deprotection sequence.

One of the first functionalized substrates subjected to the asymmetric P–H addition promoted by metal complexes were phosphine-functionalized alkenols, viz., 3-diphenylphosphinobut-3-en-1-ol and 2-diphenylphosphinoprop-2-en-1-ol (Scheme 7) [54]. The target was the diphosphine ProPhos which had previously been prepared by tedious organic manipulations extending to 14 steps from a chiral pool consisting of malic and L-ascorbic acid [55, 56]. The hydrophosphination reaction employing (*R*)-**1** was carried out as shown in scheme 7 and showed excellent selectivity in the case of 3-diphenylphosphinobut-3-en-1-ol (four isomeric products in the ratio 2:18:1:4) and moderate selectivity in the case of 2-diphenylphosphino prop-2-en-1-ol (1:2:5:8). Isomer **12a** was the major product in the case of 3-diphenylphosphinobut-3-en-1-ol ($n = 1$), and for 2-diphenylphosphinoprop-2-en-1-ol ($n = 2$), **11a** and **11b** co-crystallized out. The two analogous substrates gave products that differ in the chirality at the newly formed carbon center.



Scheme 7 Asymmetric hydrophosphination of phosphine functionalized alkenols

The contrasting product stereochemistry may be due to the formation of a pseudo 5-coordinated intermediate with an axial Pd–O interaction as seen in the solid-state X-ray structure of the longer chain complex (*R*)-**10** ($n = 2$) (Fig. 1).

The Pd–O interaction therefore imposes a steric directing effect during the subsequent nucleophilic attack. This Pd–O interaction is less favorable in the shorter chain complex ($n = 1$) and leads to a significantly lower chiral discrimination.

This protocol can be extended to cyano-, ester-, and keto-functionalized monophosphines (Scheme 8). For the ester and keto protocols, the allylic and homoallylic monophosphines were synthesized via a versatile one-pot process [57]. Subsequent asymmetric hydrophosphination of the coordinated substrates promoted by the chiral auxiliary gave the corresponding functionalized chiral 1,2-bis(diphenylphosphino)ethane and 1,3-bis(diphenylphosphino)propane ligands in high yields. For the *cis*-ester-functionalized monophosphine palladium complex ($n = 1$), only two regioisomeric products were observed and isolated in 87% yield with *S* absolute configuration being formed exclusively at the newly generated carbon center. For the *trans*-ester monophosphine palladium complex ($n = 1$), three isomeric products were formed with again *S* absolute stereochemistry at the newly formed chiral center with absolute stereoselectivity of 10:1. For the analogous *trans*-keto monophosphine palladium complex ($n = 1$), the hydrophosphination gave three isomers in the ratio 1:16:2. The major regioisomers, again with

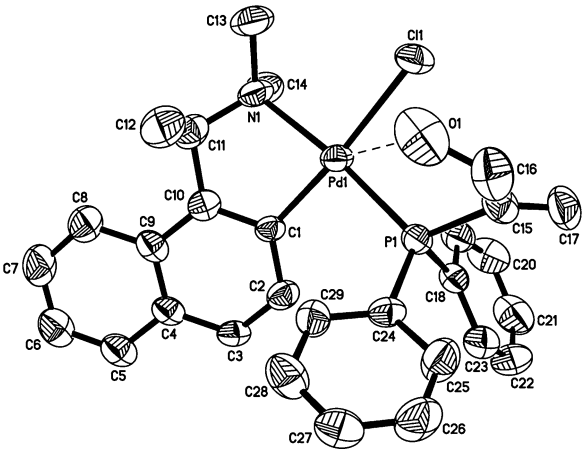
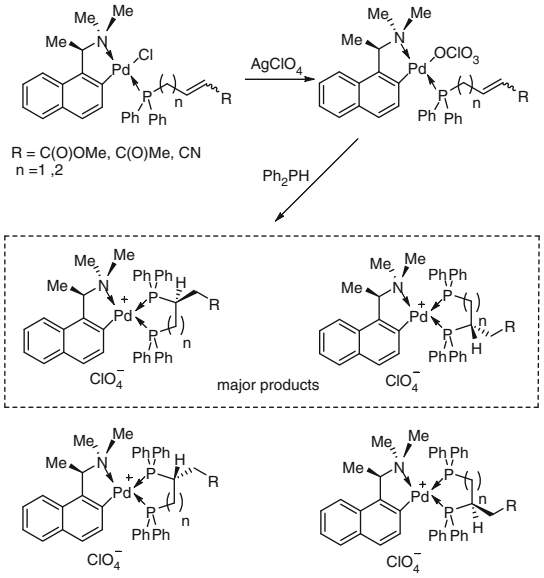


Fig. 1 Molecular structure of (R)-10 showing the Pd-O interaction. Reprinted with permission from Pullarkat SA, Yongxin L, Tan GK, Leung PH (2006) Inorg Chem 45:7455. Copyright 2006 American Chemical Society



Scheme 8 Asymmetric hydrophosphination of functionalized monophosphines

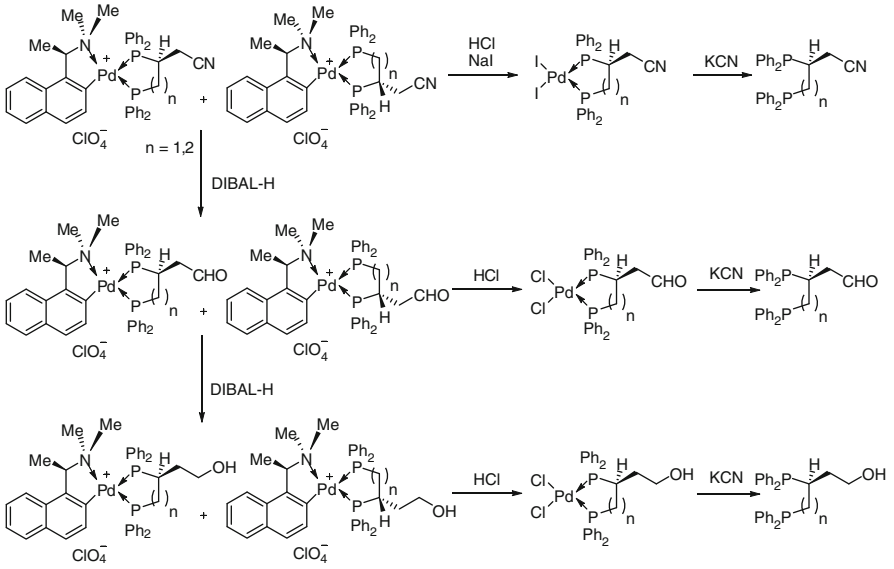
S absolute stereochemistry indicative of the efficacy of stereocontrol by the template complex, could be isolated in 78% yield. Similarly for the *trans*-ester monophosphine palladium complex ($n = 2$), four products were formed with stereoselectivity of 4:1, and the major regioisomeric products with *R* absolute

configuration were isolated in 66% yield. For the *trans*-keto palladium complex ($n = 2$), the isomers were formed with stereoselectivity of 7:1, and the major regioisomers with R absolute configuration at C isolated in 75% yield.

The asymmetric hydrophosphination of the cyano-functionalized phosphine has also been undertaken in view of the potential for further manipulation of the cyano moiety to formyl and hydroxyl functionalities [58]. This will serve as an elegant method for accessing these functionalized diphosphines. The diastereoselective hydrophosphination reactions of the *cis*-cyano-functionalized phosphine complex ($n = 1$) gave the chiral 1,2-bis(diphosphino)ethane products in high yield (90%) and stereoselectivity (*S* isomer formed exclusively). For the *trans* analogue, the absolute stereoselectivity was 10:1 with the *S* isomer being the major product.

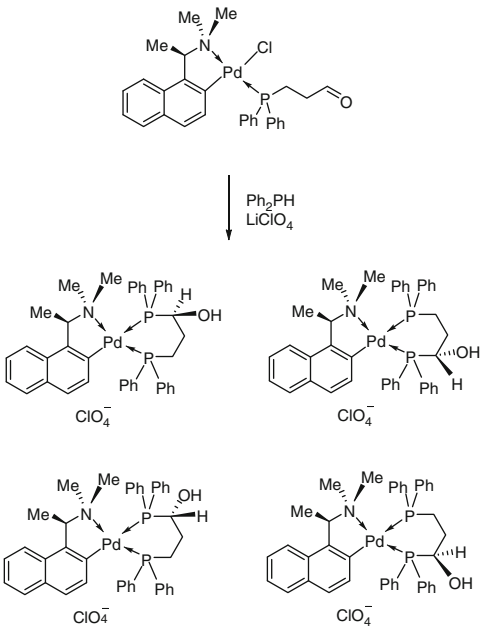
The subsequent organic transformations of the cyano group of the chelated diphosphine product posed unique challenges due to the inherent kinetic and chemical instability issues. However, reduction using DIBAL-H yielded the formyl-functionalized complexes, and further reduction of the regioisomers with DIBAL-H could chemoselectively yield the hydroxyl-functionalized products (Scheme 9). During all these manipulations, the stereochemical integrity of the diphosphine remains intact. This synthetic method therefore provides access to a wide range of functionalized chiral 1,2-diphosphine ligands with high enantioselectivity.

The flexibility of the protocol is not limited to the generation and subsequent transformations of functionalized 1,2-diphosphine systems in an asymmetric manner. The same methodology can also be used to access optically pure diphosphines containing the 1,3-bis(diphenylphosphino)propane backbone analogous to



Scheme 9 Organic transformations of the cyano group in the chelated diphosphine products with retention of stereochemistry

(*S*)-ChairPhos, a class of ligands that have proven to be powerful bidentate ligands in transition metal-catalyzed asymmetric reactions (Scheme 9, $n = 2$) [59]. While the chiral complex controls the stereochemistry of the intermolecular hydrophosphination reaction, the dangling functional groups probably play an important role in the activation of the C=C bonds in these long chains. The Pd–P coordination in this instance would be too far to effectively activate the olefin moieties for nucleophilic attack. Accordingly, ester-, keto-, and cyano-functionalized 1,3-diphosphines can be generated via the addition reaction. Transformations of the cyano moiety in a procedure similar to that employed for the 1,2-diphosphines to obtain formyl- and hydroxyl-functionalized 1,3-diphosphines have also been achieved [60]. As part of this library of functionalized 1,3 diphosphines, hydrophosphination of 3-(diphenylphosphino)propanal (Scheme 10) to afford hydroxyl-functionalized 1,3-diphosphines directly has also been studied [59]. This work assumes significance in view of the fact that addition of a secondary phosphine to an aldehyde is usually rather complex, as the process has been proven to be reversible, and the corresponding adducts are prone to isomerization to form phosphine oxides. Metal chelation, however, rendered the system stable, and the solution of the enantiomerically pure complex can be kept for 15 d in dichloromethane without loss of optical purity. However, the lack of stability rendered the usual ligand liberation protocol redundant in this case, unless the hydroxyl group is transformed into other functionality such as an ester prior to liberation.



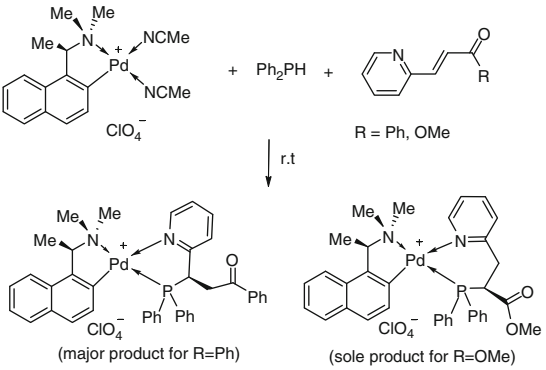
Scheme 10 Asymmetric synthesis of hydroxyl-functionalized 1,3-diphosphines

4 Asymmetric Hydrophosphination of Pyridylphosphines: Access to Chiral P–N Ligands

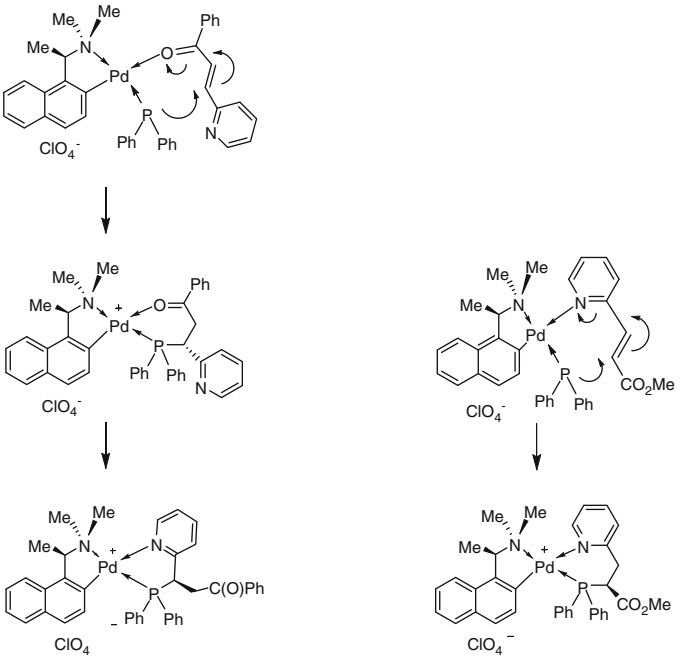
Chiral pyridylphosphines which incorporate a soft π-acceptor and a relatively harder σ-donor have been attracting interest in view of their applications in asymmetric catalytic scenarios such as allylic substitution, hydrogenation, hydrosilylation, hydroboration, etc., [61–68]. The hydrophosphination of (*E*)-1-phenyl-3-(pyridin-2-yl)-2-propenone and methyl (*E*)-3-(pyridin-2-yl)-2-propenoate has been conducted as shown in Scheme 11 [69]. Interestingly, the former gave stereoisomeric five-membered P–N bidentate products in the ratio of 8:1 (major isomer shown in Scheme 11) while the latter gave exclusively one chiral six-membered P–N chelate product.

The difference in regioselectivity seen at the site of attack of the nucleophilic phosphido moiety during its addition to the activated alkene can be explained by the difference in coordination mode of the phenyl (*E*)-1-phenyl-3-(pyridin-2-yl)-2-propenone and methyl (*E*)-3-(pyridin-2-yl)-2-propenoate. It has been previously reported that the palladium site which is *trans* to the strong π-accepting naphthylene ring show high preference toward the ketone but not the ester [70]. As shown in Scheme 12, the attack of the phosphido moiety on the *O*-coordinated ketone substrate gives the P–O chelate which subsequently rearranges into the thermodynamically more stable five-membered P–N ring. On the other hand, the *N*-coordinated ester substrate leads directly to formation of the stable six-membered P–N ring. Clearly, the unique electronic properties of the palladacycle direct the different modes of substrate coordination efficiently and generate the P–O and P–N six-membered rings with opposite configurations.

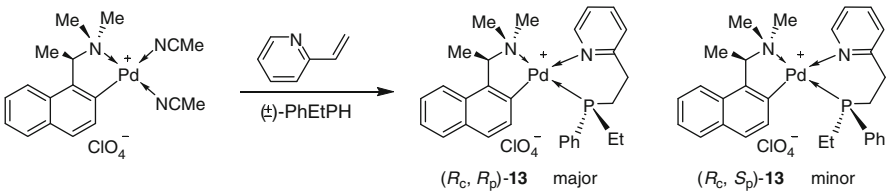
This body of work was the first efficient asymmetric synthesis of the keto- and ester-functionalized C-chiral pyridylphosphine ligands via an asymmetric hydrophosphination reaction. The methodology has also been extended to generate P chirality in such P–N ligand motifs. The reaction of 2-vinylpyridine with (±)-PhEtPH as shown in Scheme 13 proceeded smoothly and generated two



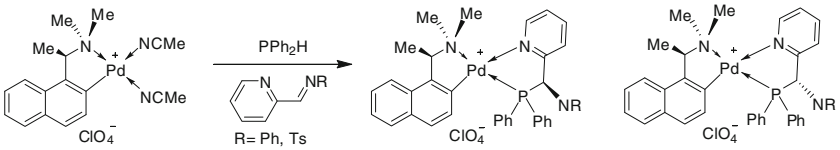
Scheme 11 Asymmetric synthesis of chiral pyridylphosphines



Scheme 12 Regioselectivity considerations during the nucleophilic attack on keto and ester functionalized substrates



Scheme 13 Asymmetric hydrophosphination of 2-vinlpyridine with PhEtPH



Scheme 14 Asymmetric addition of diphenylphosphine across a C=N bond

diastereomers in the ratio 1.5:1, and the major and minor products can be separated by a single crystallization to give the products in 51% and 31% yield, respectively [45]. The exclusive formation of the six-membered P–N ring in this case is

consistent with previous observation wherein pyridine N-coordinates to the Pd center during the course of the nucleophilic addition reaction (Scheme 12).

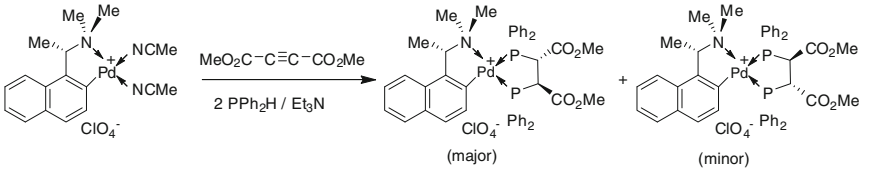
Recently it has been demonstrated that the methodology can also be used on (*E*)-*N*-(pyridin-2-ylmethylene)-based substrates wherein it involves the addition of the nucleophile across the imino C=N bonds with diastereoselectivities up to 1:20 in favor of the *S* isomer (Scheme 14) [71, 72]. The presence of the imino nitrogen in this instance is the predominating electronic factor which dictates the regioselectivity of the nucleophilic addition reaction and leads to the exclusive generation of the five-membered chelate.

5 Asymmetric Hydrophosphination Involving Other Substrate Systems and Development of a Catalytic Protocol

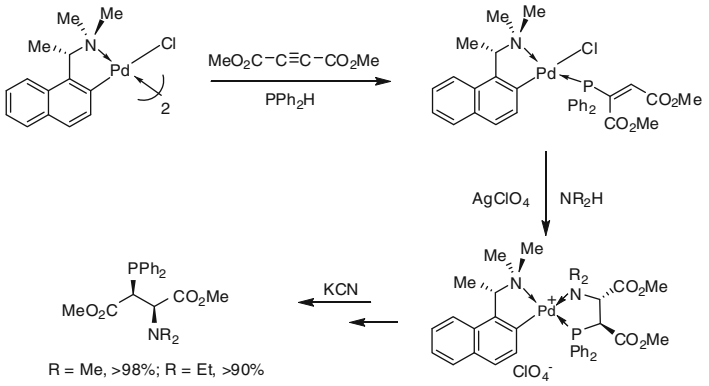
The generation of a phosphine-functionalized substrate and its coordination to the chiral metal template in order to activate the unsaturated C=C bond toward nucleophilic attack is a prerequisite for the hydrophosphination reactions seen in previous sections. However, in the case of activated alkynes such as dimethyl acetylenedicarboxylate or its diketone analogue, this pre-preparation of the phosphinoalkene is not necessary, and a direct hydrophosphination using two equivalents of diphenylphosphine in the presence of trace amounts of base was found to promote the two-stage hydrophosphination in a one-pot process with diastereoselectivity of 6:1 and in quantitative yield (Scheme 15) [73].

The one-pot synthesis of the difunctional diphosphine may also be modified to allow the synthesis of chiral heterobidentates. The addition reaction with alkynes occurs via a stepwise mechanism, and the phosphinoalkene intermediates can be generated chemoselectively when stoichiometric amount of diphenylphosphine is used. A second portion of selected coordinating nucleophile, such as dialkyl amines, can then be added directly into the reaction mixture to form the corresponding hetero-P–N bidentates in technically quantitative yields with high diastereoselectivity (19:1) (Scheme 16) [74].

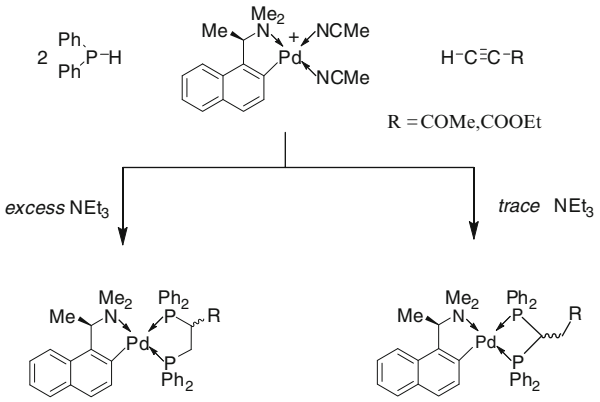
When a carboxylate or ketone-substituted alkyne was used for the hydrophosphination reaction, the corresponding monophosphine-substituted intermediate exists as a classical enol–keto equilibrium mixture, which is sensitive to the pH of the reaction. Therefore, by regulating the amount of triethylamine as a noncoordinating external base, the (1,1)- and (1,2)-addition pathways could be



Scheme 15 One-pot Asymmetric hydrophosphination of dimethyl acetylenecarboxylate



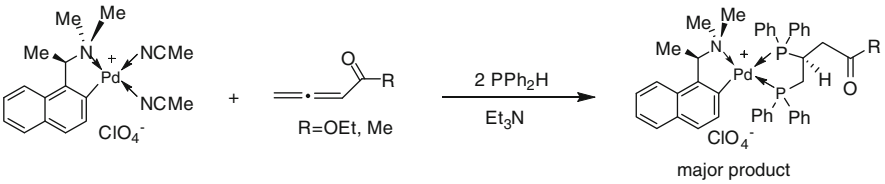
Scheme 16 Sequential hydrophosphination and asymmetric hydroamination protocol for the synthesis of P-N ligands



Scheme 17 Effect of base in the formation of 1,1 and 1,2-additions products

controlled chemoselectively [75]. In the instance of the addition of diphenylphosphine to 3-butyn-2-one, for example, (Scheme 17), the reaction can be controlled effectively to specifically yield either the (1,1)- or (1,2)-addition products depending on the amount of external base used (2 mol % vs. 20 equiv). The 1,1-addition product can be converted efficiently into the enantiomerically pure diphosphine monoxide by a simple treatment with hydrogen peroxide.

Unlike the unsaturated systems seen so far, allenes by virtue of the presence of two π-orbitals perpendicular to each other exhibit reactivities as well as selectivities which are very different from the aforementioned unsaturated systems in a catalytic scenario [76–78]. Reports on the hydrophosphination of allenes (even the non-asymmetric version) are quite rare and plagued by poor chemoselectivity [18]. The chiral metal-mediated asymmetric hydrophosphination methodology has been able



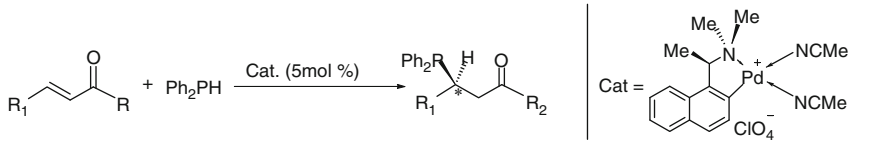
Scheme 18 Asymmetric hydrophosphination of allenes

to achieve the first reported asymmetric hydrophosphination of cumulated unsaturated bond systems as shown in Scheme 18 [79].

The presence of ester or keto functional group is a critical factor, and nonconjugated allenes tested did not undergo this hydrophosphination reaction under the same conditions. The amount of triethylamine in this instance was also found to have an impact on selectivity with 10% of amine (based on diphenylphosphine) being the optimum for achieving the desired regio- and stereoselectivity.

The flexibility and potential of this chiral auxiliary continues to show scope for expansion, and recently they have proven to be extremely efficient in certain catalytic versions of the asymmetric P–H addition process (Table 1) [80]. Very few catalytic asymmetric syntheses of chiral tertiary phosphines by hydrophosphination have been

Table 1 Palladacycle promoted catalytic hydrophosphination of enones[a]



Entry	R_1, R_2	Temp °C	Time	Yield[b] (%)	e[c] (%)
1	Ph, Ph	−80	23 h	65 (99)	98 (77)
2	Ph, 2-Naph	−80	50 h	53 (99)	94 (74)
3	2-Naph, Ph	−80	60 h	(99)	(86)
4	2-Naph, 1-Naph	−80	6 d	48 (97)	96 (57)
5	4-ClC_6H_4, Ph	−80	40 h	70 (99)	98 (77)
6	Ph, 4-ClC_6H_4	−80[d]	6 d	(96)	(57)
7	4-BrC_6H_4, Ph	−80[d]	7 d	(92)	(51)
8	4-$NO_2C_6H_4$, Ph	−80	6 d	67 (99)	88 (70)
9	3-$NO_2C_6H_4$, Ph	−80	4 d	41 (99)	85 (55)
10	4-OHC_6H_4, Ph	−80	7 d	40 (98)	99 (73)
11	4-$MeOC_6H_4$, Ph	20	40 h	(97)	(33)

[a]Conditions: 0.35 mmol Ph_2PH, 5 mol % of catalyst, 5 mL THF, 1.1 equiv of enone, 0.5 equiv of Et_3N were reacted at the given temperature, unless otherwise noted

[b]Yields of isolated products after a recrystallization. In parentheses are the yields of isolated products before recrystallization

[c]ee after a recrystallization determined from $^{31}P\{^1H\}$ NMR integration of the signals. In parentheses are the ee's before recrystallization

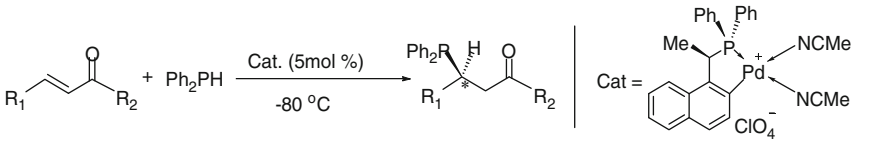
[d]Temperature raised gradually to 0°C for another day after indicated time

reported in literature [81, 82]. Among the few asymmetric catalyses reported, Pt(0)-(Me-Duphos) and Pt(0)-(diphos) complexes catalyze hydrophosphination of α,β-unsaturated esters and nitriles with low enantioselectivity [83–86], Ni(II) complex catalyzes hydrophosphination of methacrylonitrile [32, 87], and organocatalysts catalyze hydrophosphination of nitroalkenes and α,β-unsaturated aldehydes [88–91]. However, phosphine oxides, phosphine sulfides, or phosphine boranes were usually obtained as products instead of tertiary phosphines due to the fact that these phosphines are quite air sensitive and difficult to handle and achieve [92]. Reduction or removal of borane is therefore necessary in order to get the desired tertiary phosphines.

Apart from being air sensitive, the generally stable M–P coordination renders technical difficulties in the elimination of the tertiary phosphine product in catalytic process involving transition metal ions as catalysts. However, the asymmetric hydrophosphination of aromatic enones could be catalyzed by the same organopalladium (II) complex with high yields and stereoselectivity (Table 1).

It is noteworthy that some of the tertiary phosphine products could be purified to 100% optical purity by a simple recrystallization from dichloromethane/acetone.

Table 2 Improved Phosphapalladacycle catalyst for the hydrophosphination of eneones[a]



Entry	R_1	R_2	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph	Ph	2	99 (90)	98 (>99)
2	4-$NO_2C_6H_4$	Ph	2	99 (89)	98 (>99)
3	3-$NO_2C_6H_4$	Ph	8	99 (85)	96 (>99)
4	4-ClC_6H_4	Ph	4	99 (90)	98 (>99)
5	4-F C_6H_4	Ph	5	99 (91)	99 (>99)
6	4-$CF_3C_6H_4$	Ph	2	99 (91)	96 (>99)
7	4-MeC_6H_4	Ph	12	99 (90)	99 (>99)
8	4-$MeOC_6H_4$	Ph	30	99 (92)	99 (>99)
9	2-Naph	Ph	7	99 (91)	99 (>99)
10	2-Naph	4-FC_6H_4	7	99 (89)	97 (>99)
11	Ph	4-ClC_6H_4	4	99 (89)	97 (>99)
12	4-FC_6H_4	4-ClC_6H_4	5	99 (90)	97 (>99)
13	4-ClC_6H_4	4-FC_6H_4	4	99 (90)	98 (>99)

[a]Conditions: 0.30 mmol Ph_2PH, 5 mol % of cat, 5 ml THF, 1.0 equiv. of enone, 0.5 equiv. of Et_3N were reacted at −80°C, unless otherwise noted

[b]Yield was calculated from $^{31}P\{^1H\}$ NMR. In parentheses are the yields of isolated products after a single recrystallization

[c]ee was determined from $^{31}P\{^1H\}$ NMR integration of the signals. In parentheses are the ee's after a single recrystallization

From the mechanistic standpoint, the catalytic cycle is carried forward due to the labile nature of the products in the presence of excess secondary phosphine. This is consistent with the observation in which the generally inert P–Pd coordination in the *trans* N–Pd–P moiety becomes kinetically labile when it is treated with even slight excess of tertiary phosphine ligand. Following this concept, a new phosphapalladacycle-based C–P catalyst has been recently developed (Table 2) [71, 72]. The new C–P catalyst is indeed found to be superior to its C–N analogue, as the substrate–Pd coordination is weaker in the *trans* P–Pd–P coordination moiety and the P–Ph groups in the catalyst are able to control the stereochemistry of the addition reactions better than the N–Me counterparts. Selected examples of hydrophosphination reactions catalyzed by this phosphapalladacycle catalyst is given in Table 2.

In summary, asymmetric P–H additions leading to the direct enantioselective/diastereoselective formation of optically pure mono- and polydentate tertiary phosphines are thus a field that has more room for development. This is true especially in the realm of catalytic P–H additions as illustrated in the preceding sections wherein design of better catalysts is currently attracting much attention. It is thus foreseeable that in the near future even more types of enantiomerically pure tertiary phosphines with a large range of functionality will be soon available via the asymmetric hydrophosphination reaction.

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Recent Progress in Transition Metal-Catalyzed Addition Reactions of H–P(O) Compounds with Unsaturated Carbon Linkages

Masato Tanaka

Abstract Organophosphorus compounds are playing important roles in our daily life covering a wide range of applications from medicinal use to flame-retardant materials. Although classical synthetic methodologies are still used to synthesize them, the addition reactions of H–P(O) compounds such as *H*-phosphonates, *H*-phosphinates, and *sec*-phosphine oxides have been developed to partially replace the classical methods and are envisioned to be an indispensable tool in the near future. This chapter intends basically to provide recent progress in the field, but not a full scope on the reaction since the same subject was already written by the author in 2004.

Keywords *H*-phosphinate · *H*-phosphonate · Hydrophosphinylation · Hydrophosphorylation · Secondary phosphine oxide

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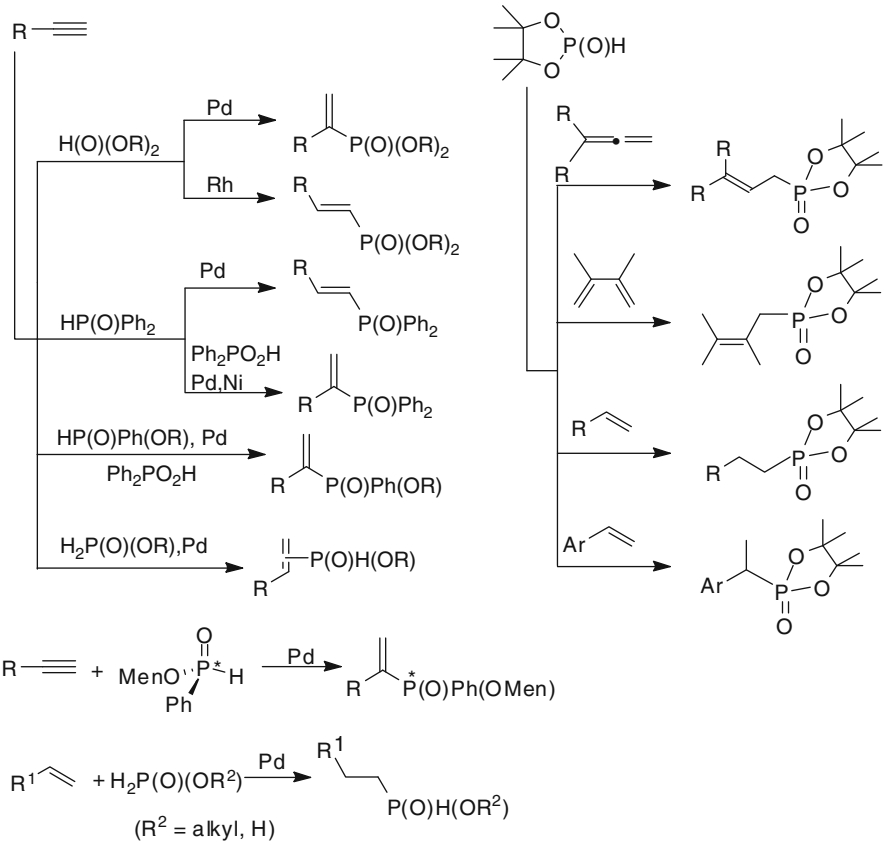
1 Introduction

Synthesis of organophosphorus compounds still depends on the classical methodologies such as Michaelis–Arbuzov reaction, Grignard reactions, and radical addition of H–P compounds. However, since the middle of 1990s, transition metal-catalyzed addition of H–P(O) compounds to unsaturated carbon linkages has become a powerful alternative. The new procedure is particularly useful in terms of regioselectivity, since the long-known radical addition to unsaturated carbon linkages produces linear products mainly [1]. The review article published in 2004 [2] summarized the development since the first scientific report on this type of reactions, covering the reactions of *H*-phosphonates, *H*-phosphinates, hypophosphorous acid derivatives, and *sec*-phosphine oxides with alkynes, alkenes, and dienes (Scheme 1). This chapter intends to cover the progress since the review although radical and base-catalyzed processes will not be mentioned. Major efforts made over the period comprise detailed understanding of the catalysis, elucidation



Scheme 1 Major H–P(O) bond addition reactions developed by 2004

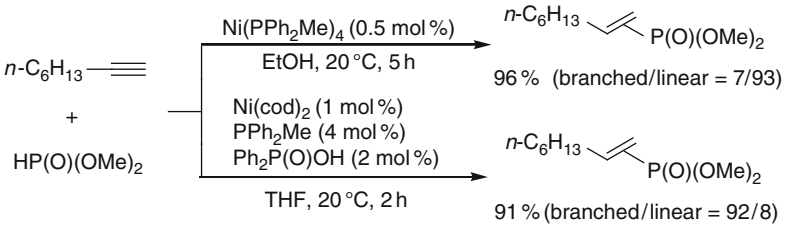
of the mechanism, development of new catalysts, expansion of the scope of the reaction (new substrates and the reagents), and application of the catalysis to prepare useful products. This chapter is categorized basically according to the structures of the substrates and reagents. Occasionally, however, the categorization will be neglected since it is not always easy to distinctly separate. The reaction has been the subject of several review articles [3–6].

2 Addition Reactions of *H*-Phosphonates and Related Reagents with Alkynes

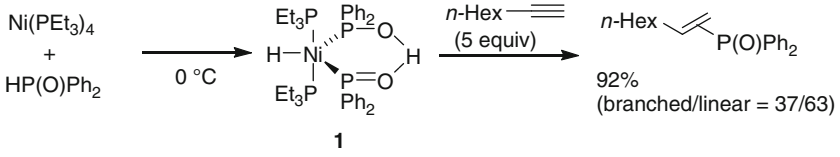
According to the detailed results [7] on the nickel-catalyzed addition of *H*-phosphonate to terminal alkynes [8], the reaction of $HP(O)(OMe)_2$ with 1-octyne run in ethanol at room temperature gives the linear isomer as major product (Scheme 2). As is anticipated in view of the influence of acidic additives found with palladium catalysts [9], the same reaction run with diphenylphosphinic acid added as an additive reverses the regioselectivity (branched/linear = 92/8). HP(O)Ph(OEt) and $HP(O)Ph_2$ behave similarly.

In mechanistic study, the species **1** (Scheme 3), generated upon treatment of $Ni(PEt_3)_4$ with $Ph_2P(O)H$ (2 equiv.) at 0°C, reacts readily with 1-octyne to afford the same products as in the catalytic reaction. Species **1** appears to adopt a trigonal bipyramidal configuration, but has not been characterized by X-ray analysis.

Beletskaya and coworkers have made a detailed look at the catalysis by palladium and nickel [10]. As has been well known, palladium-catalyzed addition of $HP(O)(OEt)_2$ with aryl- and heteroarylalkynes proceeds to form branched products. As far as phenylacetylene is concerned, the highest regioselectivity is achieved when



Scheme 2 Ni-catalyzed hydrophosphorylation of 1-octyne in the absence and presence of $Ph_2P(O)OH$



Scheme 3 Intermediate in Ni-catalyzed hydrophosphorylation

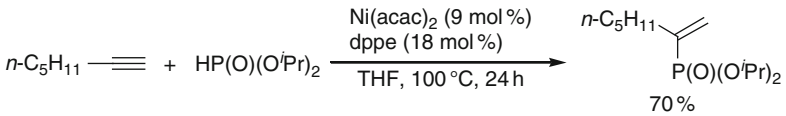
dppb ligand is used. An attempted reaction of $HP(O)(OSiMe_3)_2$, in view of easy transformation of the possible silyl ester product to free acid, failed. Although they have made mechanistic arguments on the two possibilities, either Pd–H or Pd–P(O) insertion, they have not given a conclusion.

They have also examined in detail the effect of reaction variables, solvents, and additives such as NEt_3, γ-terpinene, and various acids, in the palladium-catalyzed reaction of $HP(O)(O^iPr)_2$with 1-heptyne to search for an optimized procedure [11]. Then, they ran a series of reactions of $HP(O)(O^iPr)_2$ and longer-chained congeners with various alkynes using $Pd_2(dba)_3$ (3 mol%), Ph_3P (12 mol%, P/Pd = 2), and an acidic additive CF_3COOH, resulting in preferential formation of branched products.

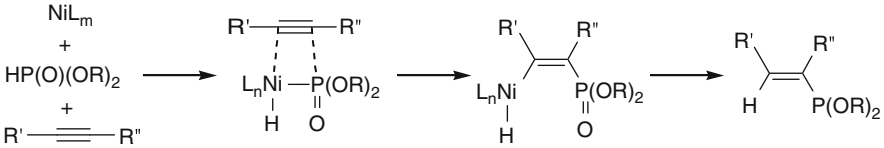
Nickel-catalyzed addition of *H*-phosphonates with alkynes was also revisited using mainly $HP(O)(O^iPr)_2$ and 1-heptyne [12]. Among the catalyst systems tested, the combination of $[Ni(acac)_2]$ ($Ni(acac)_2$ can be in situ reduced to Ni(0); see [13]) and dppe appears best performing and affords branched products as major products (Scheme 4), at ≥100°C depending on the structures of *H*-phosphonate and alkyne. Use of monophosphines and other diphosphines did not display catalytic activity.

A mechanistic possibility involving coordination of the C≡C bond to the Ni center followed by external attack of *H*-phosphonate in its P(III) tautomeric form is excluded because of the *cis*-adduct formation. Mechanistic study by DFT calculation on the insertion of a C≡C linkage into a Ni-P(O) bond has suggested that the process is thermodynamically feasible (Scheme 5). They considered two possibilities, one involving dissociation of a phosphorus end in dppe and the other taking place without dissociation. The former appears kinetically favored, and the TS involved in the latter process appears to be less favored from the kinetic view point. DFT analysis to compare hydronickelation and phosphonickelation will be discussed in the following section.

Comparison of the catalytic performance of Pd and Ni complexes in the addition of $HP(O)(O^iPr)_2$ with 1-heptyne has also been examined in detail [14]. Although the performance varies depending on the structures of the catalyst precursors and the substrates, the variation of the performance may have come from the complication due to (a) the difference in the ease of generation of active species from



Scheme 4 Ni-dppe-catalyzed hydrophosphorylation of 1-heptyne

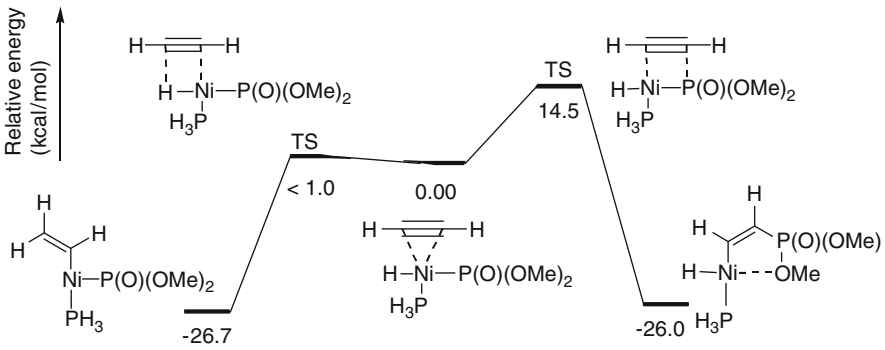


Scheme 5 A possible pathway of Ni-catalyzed hydrophosphorylation

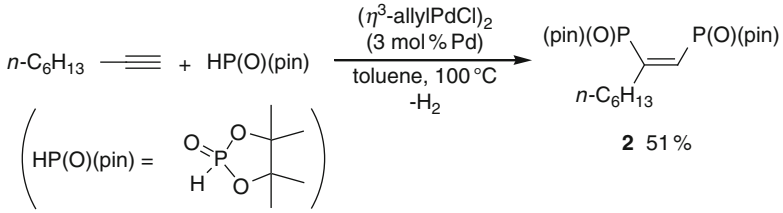
precursors and (b) involvement of side reactions such as oligomerization. They have concluded that the genuine catalytic performance of Ni- and Pd-based systems estimated after excluding these two factors is quite comparable. DFT calculation to compare hydrometalation and phosphometalation for the nickel catalyst (Scheme 6) has suggested that hydronickelation appears to be a no barrier spontaneous process while phosphonickelation has to go through a low barrier, although the process is also exothermic.

Further theoretical study to clarify alkyne insertion into various M–P and M–H bonds generated as intermediate in H–P bond addition reactions has suggested the following general trends [15]; (1) insertion into M–H is more facile and (2) the relative reactivity decreases in the orders of Ni > Pd > Rh > Pt and PR_2 > $P(O)R_2$ > $P(O)(OR)_2$. These conclusions appear to agree with most of the experimental results, although the detailed mechanism in real catalysis can be variant, depending on the specific cases.

HP(O)(pin), a five-membered *H*-phosphonate, reacts with terminal alkynes to afford dehydrogenative double addition products in the presence of $PdCl_2$ or other Pd(II) compounds used as precatalyst without phosphine ligand at 100°C for 16–22 h (Scheme 7) [16]. Although a similar reaction of $HP(O)Ph_2$ forming (*E*)-adducts has already been reported (Sect. 4) [17], the new reaction of pinacol phosphonate using Pd(II) is totally different in which it affords (*Z*)-adducts, for instance, **2** from *n*-octyne. Simple *H*-phosphonate like $(MeO)_2P(O)H$ does not react



Scheme 6 Thermochemical profile of hydrometalation and phosphometalation

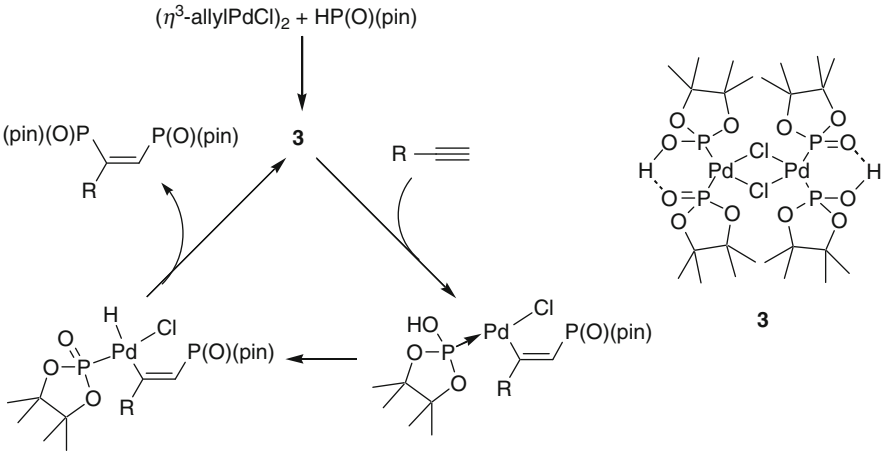


Scheme 7 Dehydrogenative double phosphorylation of alkyne

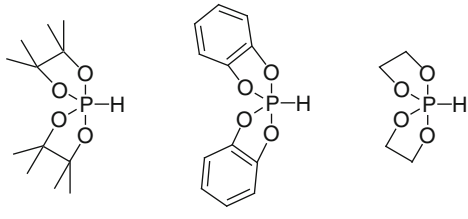
under the same conditions. The reactions using $Pd(PPh_3)_4$ or $PdCl_2/Ph_3P$ (PPh_3/Pd = 4) ends up with simple addition, and the double addition product is not formed as major product. As anticipated by the stoichiometry of the reaction, addition of hydrogen acceptors such as styrene, acrylonitrile, and methyl acrylate boosts the yield of **2** up to 74%.

A mechanism involving a Pd(II)/Pd(IV) catalytic cycle is proposed for the dehydrogenative double addition (Scheme 8). Isolation of dimeric Pd(II) complex **3** upon treatment of HP(O)(pin) with (η^3-allylPdCl)$_2$ and its reaction with 1-octyne forming 76% of **2** support the mechanism. A model complex of a structure somewhat different from **3** shows phosphopalladation with 1-octyne, which is provided to rationalize the transformation from **3** to **2** via the elemental steps shown in Scheme 8.

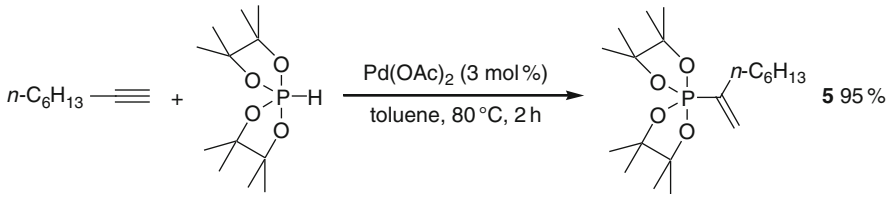
Hypervalent *H*-spirophosphorane **4a** has been found to add to alkynes (Schemes 9 and 10) [18]. However, *H*-spirophosphoranes **4b** and **4c** having catecholate and ethylene glycolate residues in place of pinacolate do not furnish similar adducts even under forcing conditions. For instance, a reaction of 1-octyne with **4a** effected using 3 mol% $Pd(OAc)_2$ at 80°C for 2 h forms hypervalent adduct **5** in 95% yield. Other alkynes, inclusive of internal ones, also afford >73% yields



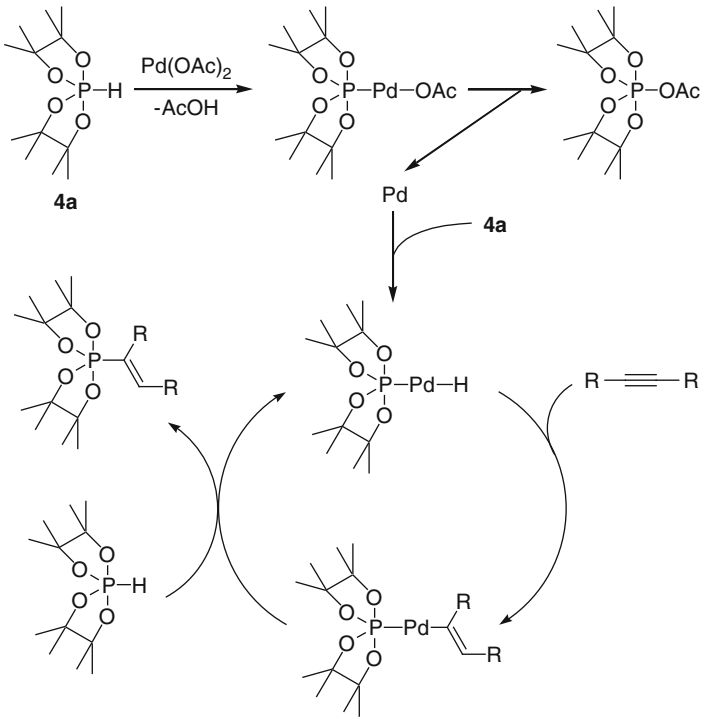
Scheme 8 Proposed mechanism of dehydrogenative double phosphorylation of alkyne



Scheme 9 Structure of hypervalent *H*-spirophosphoranes



Scheme 10 Addition reaction of *H*-spirophosphorane with terminal alkynes



Scheme 11 Proposed mechanism of the reaction of *H*-spirophosphorane with terminal alkynes

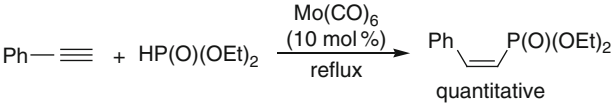
(≥96% regioselectivities), while alkenes are unreactive. The products can be hydrolyzed to plain alkenylphosphonates or further to alkenylphosphonic acids in 77–86% yields. A mechanism via hydropalladation shown in Scheme 11 is proposed.

Hydrophosphorylation of alkynes via external attack of *H*-phosphonate to an (alkyne)metal complex is a possible pathway, although the possibility has been concluded to be less likely as far as the nickel-catalyzed reaction is concerned [12]. However, such a process appears to proceed in early transition metal carbonyl-catalyzed reactions [19]. For instance, refluxing a mixture of phenylacetylene, $HP(O)(OEt)_2$, and $Mo(CO)_6$ (10 mol%) affords the *trans*-addition product

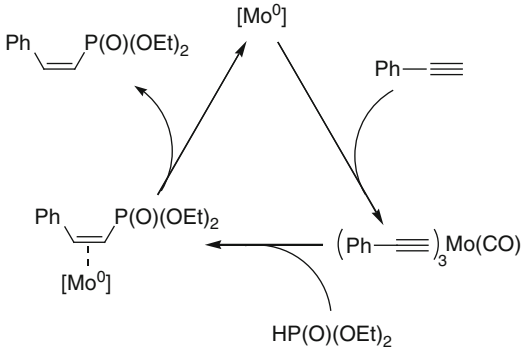
quantitatively (Scheme 12), suggesting the mechanism illustrated in Scheme 13, which involves an external nucleophilic attack of the *H*-phosphonate. An intermediate (alkyne)Mo(CO) species can be isolated. Due to the lack of the details of the reaction, however, it is premature to further discuss the mechanism.

Due to the successful development of the catalyzed hydrophosphorylation, its extension to functionalized alkynes is becoming of interest. Nickel-catalyzed addition of *H*-phosphonate (and also *H*-phosphinate and *sec*-phosphine oxide) to propargylic alcohols is an interesting example, as discussed later (Sect. 4).

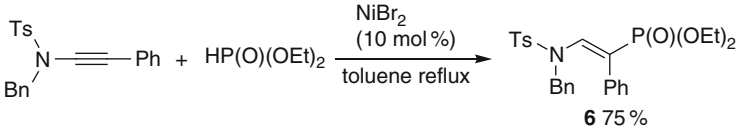
Another interesting example is nickel-catalyzed addition of *H*-phosphonate to ynamides [20]. The reaction of $HP(O)(OEt)_2$ shown in Scheme 14 does not proceed in the presence of potential promoters (catalysts) such as TfOH, AIBN, and Lewis acidic metal salts of Ag, Au, Cu, and Pt. $Pd(PPh_3)_4$ does display a weak activity, but $NiBr_2$ has proved to be the catalyst of choice affording (*E*)-aminovinylphosphonate **6** in 75% isolated yield under optimized conditions in refluxing toluene. Other *H*-phosphonates also react similarly, showing that $HP(O)(O^iPr)_2$ is most reactive giving 97% yield under nearly the same conditions, while $HP(O)(OPh)_2$ is totally unreactive. As for the ynamides, various aromatic ones can participate in the reaction successfully, but an alkyl ynamide affords a much less yield.



Scheme 12 Mo-catalyzed hydrophosphorylation of terminal alkynes



Scheme 13 Proposed mechanism of Mo-catalyzed hydrophosphorylation

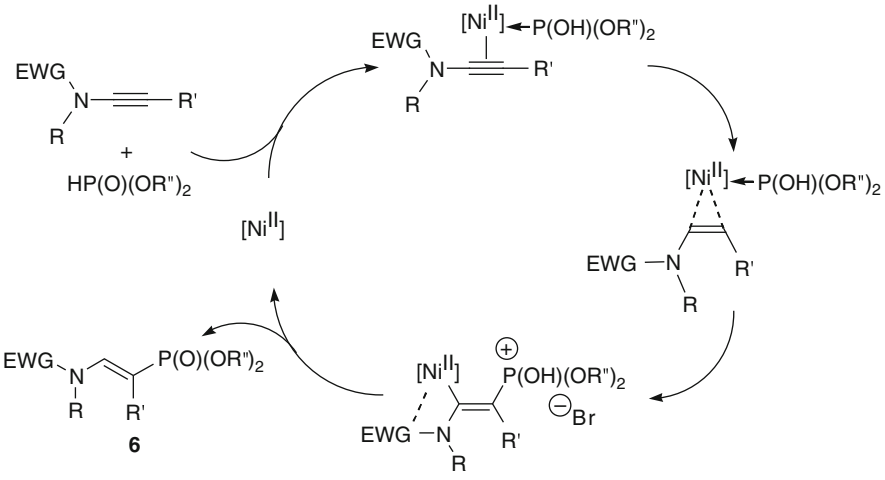


Scheme 14 $NiBr_2$-catalyzed hydrophosphorylation of ynamide

Since the reaction is efficiently promoted by Ni(II) bromide, the mechanism is envisioned to be very much different from those catalyzed by Pd(0) and Ni(0). Presumably, an alternative mechanism shown in Scheme 15, in which $NiBr_2$ works as a Lewis acid, is most probable.

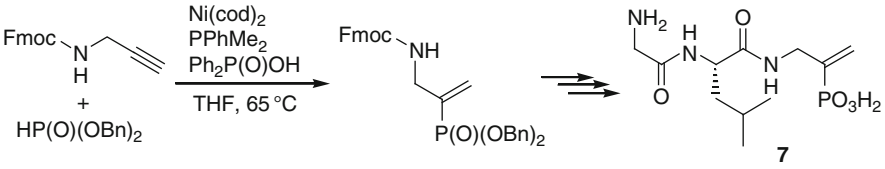
Compound **7**, a proposed structure for the antibiotic A53868, has been synthesized via a sequence of reactions involving nickel-catalyzed hydrophosphorylation of a propargyl amine derivative in the presence of diphenylphosphinic acid (Scheme 16) [21]. Although the compound is not identified with the natural A53868, it also displays antimicrobial activity against *Escherichia coli*.

Another synthetic application starting with functionalized alkynes is the tandem addition-cyclization process. Such processes in the presence of radical initiators have been reported. The first metal-catalyzed version is exemplified by the following experiments [22]; thus, when 1,6-heptadiyne is treated with $HP(O)(OMe)_2$ in the presence of $Pd(OAc)_2$ and dppben [1,2-bis(diphenylphosphino)benzene] at 130°C, cyclized product **8** is formed in 76% yield (Scheme 17). *N*,*N*-dipropargyl-*p*-tosylamide reacts similarly, but the major product is pyrrole derivative **9** due to extensive double bond isomerization. Extension to *H*-phosphinate and *sec*-phosphine oxide is also

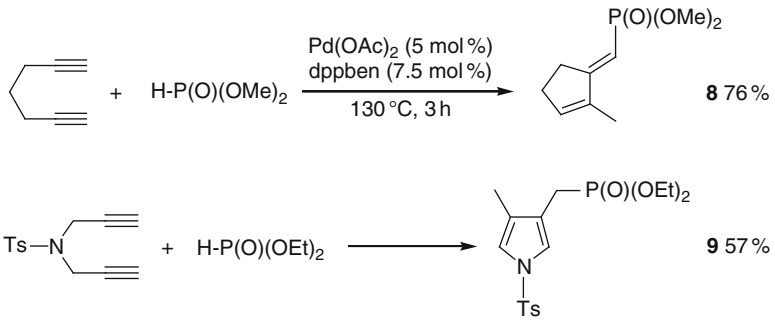


(EWG = Ts or other electron-withdrawing groups)

Scheme 15 Proposed mechanism of $NiBr_2$-catalyzed hydrophosphorylation of ynamide



Scheme 16 A synthetic application of Ni-catalyzed hydrophosphorylation



Scheme 17 Tandem addition-carbocyclization involving hydrophosphorylation

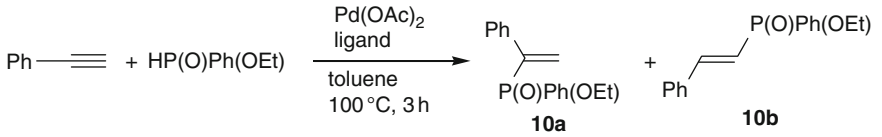
possible. These reactions are not so high yielding due to the formation of various side products. However, addition of Brønsted acids like $Ph_2P(O)OH$ in the reaction of $HP(O)Ph_2$ improves the yields dramatically (Sect. 4).

3 Addition Reactions of *H*-Phosphinates and Related H–P(O) Compounds with Alkynes

The addition reaction of *H*-phosphonate with terminal alkynes in the presence of a monodentate phosphine-palladium complex proceeds to form branched products, while the reaction of $HP(O)Ph_2$ gives linear products unless acidic promoters such as $Ph_2P(O)OH$ is present in the reaction system. Because of the conflicting nature of branched-directing alkoxy and linear-directing phenyl groups bound to the phosphorus center, the addition of ethyl phenylphosphinate HP(O)Ph(OEt) ends up with a nonselective mixture of the possible two isomers. Interestingly, however, highly branched-selective addition has been realized simply using dppe and related ligands in the place of monodentate phosphines (Scheme 18) [23]. It is also interesting to note that the reaction using a large excess of P^tBu_3 in the place of dppe in toluene or run using PPh_3 in ethanol forms the linear product preferentially. The new recipe using dppe is applicable to the reaction of $HP(O)Ph_2$ to switch the regioselectivity from the linear to the branched (Sect. 4).

CuI (10%) in conjunction of amine ligands, typically ethylenediamine, catalyzes the addition of Ph(EtO)P(O)H to phenylacetylene to afford the linear product **10b** in 82% yield with >99% regioselectivity (Scheme 19) [24]. The same procedure also works for *sec*-phosphine oxides (Sect. 4).

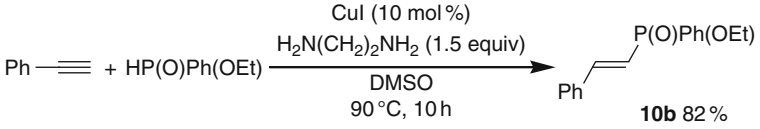
Hydrophosphorylation of alkenes and alkynes with phosphinic acid derivatives such as alkyl phosphinates [$H_2P(O)(OR)$] and anilinium phosphinate [$PhNH_3{\cdot}OP(O)H_2$] is successfully catalyzed by palladium complexes, in particular those ligated by xantphos and dppf [25]. Polymer-bound palladium catalyst **11** has proved to catalyze the same reactions with phosphinic acid to give good yields, although the



ligand(P / Pd)	yield	
	10a	**10b**
PPh_3 (3)	52	28
dppe (3)	89	1
xantphos (3)	79	16
P^tBu_3 (20)	10	82
PPh_3 (3)*	13	57

*Run in ethanol

Scheme 18 Ligand effect in hydrophosphorylation of phenylacetylene with ethyl phenylphosphinate

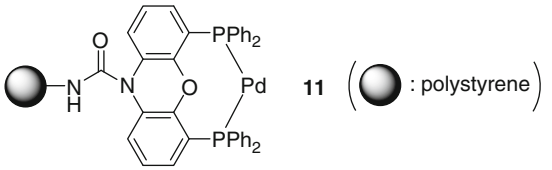


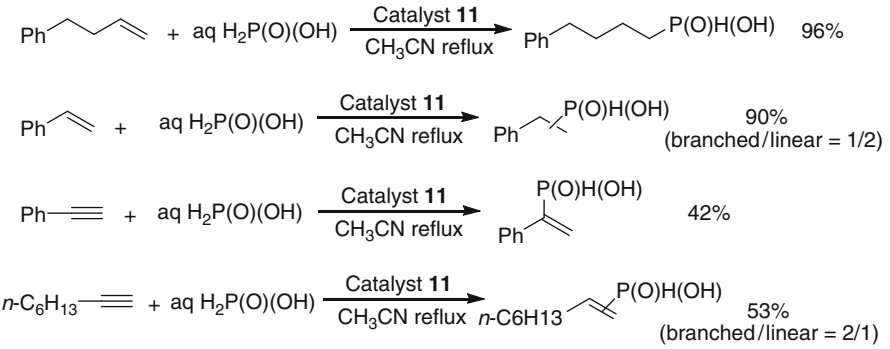
Scheme 19 Cu-ethylenediamine-catalyzed hydrophosphorylation of phenylacetylene with ethyl phenylphosphinate

scope of alkenes and alkynes as substrates is somewhat narrow as compared with homogeneous counterparts (Scheme 20) [26].

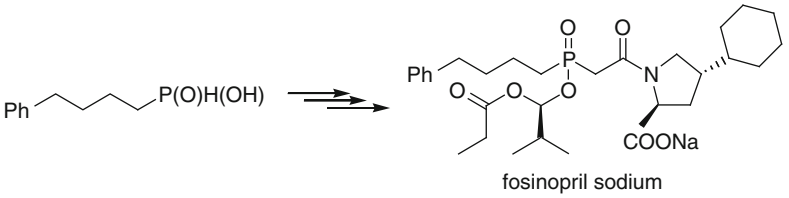
In view of reusability of the catalyst and easy separation/purification of the products, the new procedure is advantageous in practical applications, e.g., the synthesis of fosinopril sodium (Scheme 21).

Although nickel complexes are able to catalyze the addition of alkyl phosphinates to alkenes and furnish acceptable yields under optimized conditions, palladium catalysts are generally better in performance. In contrast, for alkynes, both terminal and internal, nickel catalysts, inclusive of phosphine-free NiX_2 (X=Cl, Br, I), have proved to promote the reaction efficiently [27], whereas palladium catalysts are poor in the reaction of internal alkynes. The Ni-catalyzed addition of alkyl phosphinates to internal alkynes proceeds under rather mild conditions (refluxing CH_3CN, 3 h) even in the presence of moisture and air (Scheme 22). Terminal alkynes also undergo the addition reaction, but they furnish a mixture of regioisomers. Microwave irradiation is beneficial to reduce the reaction time to a few minutes. Mechanistic detail has not been disclosed yet. $H_2P(O)(OR)$ is likely to reduce NiX_2 to catalytically active Ni(0) species, which can be ligated by alkyl phosphinate present in the reaction mixture. The reaction of $D_2P(O)(OEt)$ confirms that *cis*-addition has taken place.

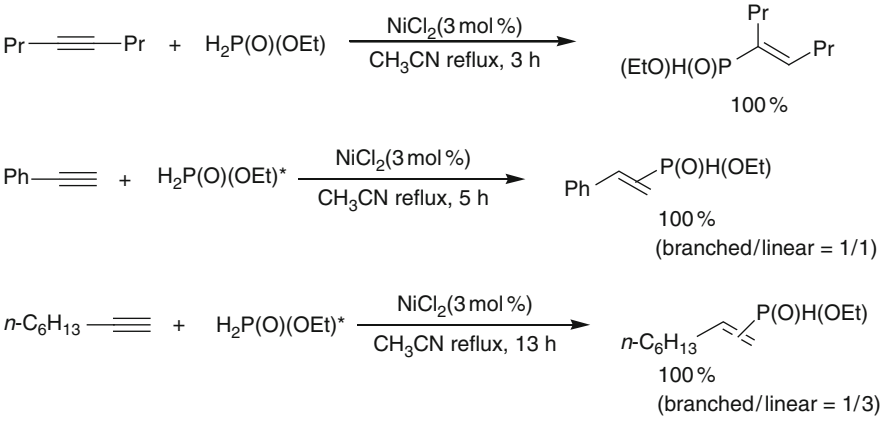




Scheme 20 Use of polymer-bound palladium catalyst in hydrophosphorylation

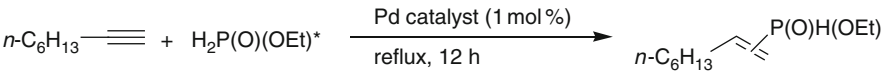


Scheme 21 A synthetic application of polymer-bound palladium catalyst to hydrophosphorylation



(*Generated by treating $H_2P(O)(OH)$ with $(EtO)_3Si(CH_2)_3NH_2$ and CF_3COOH)

Scheme 22 Ni-catalyzed addition of ethyl phosphinate with alkynes



catalyst	solvent	branched/linear	total yield (%)
$Pd_2(dba)_3$ + xantphos	CH_3CN	1/10	99
$Pd_2(dba)_3$ + dppf	toluene	16/1	100

* Generated in situ by treating $H_2P(O)(OH)$ with $(EtO)_3Si(CH_2)_3NH_2$ and CF_3COOH

Scheme 23 Pd-catalyzed addition reaction of ethyl phosphinate with terminal alkynes

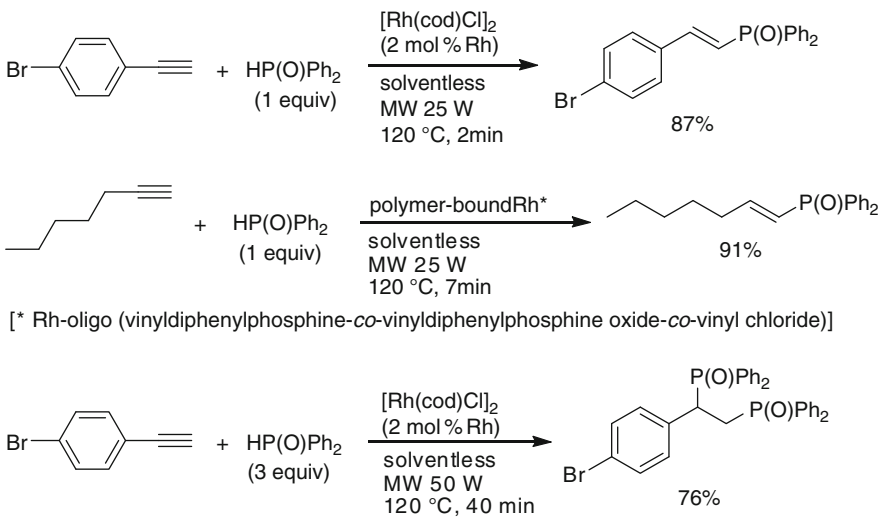
Unlike the high reactivity of alkyl phosphinates, both phosphinic acid (hypophosphorous acid, H_3PO_2) and its anilinium salt fail to undergo the nickel-catalyzed reaction efficiently.

Using 1-octyne as a probe, the regioselectivity in palladium-catalyzed addition of ethyl and butyl phosphinates was examined using various phosphine ligands (Scheme 23) [28]. The highest linear selectivity can be seen using $PdCl_2$-xantphos in CH_3CN, while $Pd_2(dba)_3$-dppf in toluene has proved to be most branched selective. There is no clear trend in the regioselectivity depending on the bite angle of the ligand. Reactions of various terminal alkynes have revealed that more electron-donating substituents favor the formation of the branched products, while electron-withdrawing substituents favor the linear isomers, although the results can be variant, depending on the solvent and the ligand.

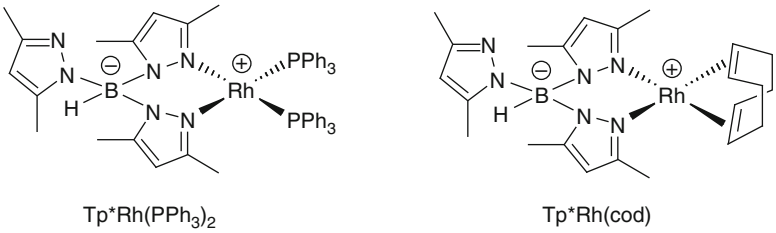
4 Addition Reactions of *sec*-Phosphine Oxides with Alkynes

Rhodium-catalyzed addition of $HP(O)Ph_2$ to terminal alkynes is an efficient process forming linear adducts [29]. Under solvent-free and microwave irradiation conditions, the reaction proceeds efficiently to give the adducts (>75% yields) in a few minutes (1.6 mol% of homogeneous or polymer-bound rhodium catalyst, microwave conditions = 25 W, temp = 120°C) (Scheme 24) [30]. When alkynes are allowed to react with 3 equiv. of $HP(O)Ph_2$ in the presence of 2 mol% of the catalyst, double addition proceeds to give satisfactory yields of dppe oxide derivatives, typically in 40 min at 120°C. The first addition is promoted by the catalyst, but the second is an uncatalyzed thermal process, in this case facilitated by the microwave irradiation. Similar double addition, reported using $Pd(PPh_3)_4$ by Lin and coworkers, requires longer reaction times (19–71 h, 110°C) [31].

Further study on the rhodium-catalyzed reaction under microwave irradiation has disclosed the effect of the structure of starting diarylphosphine oxides and alkynes on the selectivity and on the competition with oligomerization and/or polymerization of alkynes [32]. Terminal alkynes are reluctant to undergo hydrophosphinylation



Scheme 24 Rh-catalyzed microwave-promoted hydrophosphinylation with diphenylphosphine oxide



Scheme 25 Trispyrazolylborate rhodium complexes for hydrophosphinylation with diphenylphosphine oxide

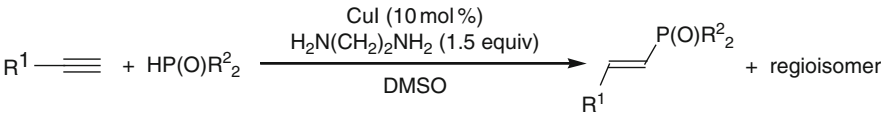
with sterically demanding phosphine oxides, such as dimesitylphosphine oxide, and mainly give oligomers and/or polymers of the alkynes.

Various new catalysts, some of which are superior to the existing ones, have been documented.

Tp*Rh(PPh_3)$_2$ [Tp*=hydrotris(3,5-dimethylpyrazolyl)borate] displays high catalytic performance in hydrothiolation of alkynes to afford branched adducts. The complex and a related complex Tp*Rh(cod) (Scheme 25) have proved to be linear-selective in the addition reaction of HP(O)Ph_2 to terminal alkynes [33]. Their activity is somewhat low as compared with RhCl(PPh_3)$_3$, giving, for instance, 51% yield in the reaction with 1-octyne (3 mol% of Tp*Rh(cod), 110°C, 3 h). When Tp*Rh(PPh_3)$_2$ is exposed to 10 equiv. of HP(O)Ph_2 for 12 h at room temperature, an unusual dinuclear complex is generated. However, its role in the catalysis is ambiguous.

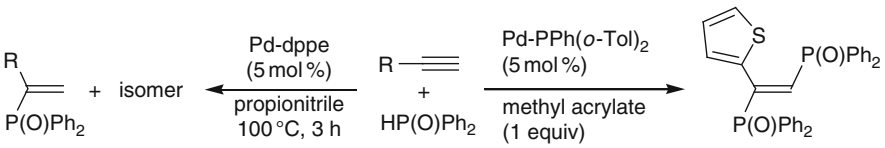
As already described (Sect. 2), copper catalysts, typically CuI, combined with ethylenediamine, catalyze addition reactions of HP(O)Ph(OEt) [24]. These catalysts are active as well in hydrophosphinylation with not only $HP(O)Ph_2$, but also $HP(O)(CH_2Ph)_2$, a dialkyl phosphine oxide that has been known to be much less reactive than diarylphosphine oxides (Scheme 26). PhC≡CH appears to be an exceptionally reactive alkyne, but other alkynes, inclusive of diphenylacetylene, also participate in the reaction under more forcing conditions. The yields are acceptable in most cases, but unfortunately the major products are linear adducts, which can be synthesized by radical addition. Functional groups such as OH and C=C are tolerated.

The Pd-dppe catalyst, which is highly branched-selective in the addition of *H*-phosphinate [23], has also proved to induce branched-selective hydrophosphinylation with $HP(O)Ph_2$ (Scheme 27) [17]. Thus, the reaction of *p*-tolylacetylene with $HP(O)Ph_2$ using $Pd(OAc)_2$ (5 mol%) and dppe (1.5 equiv. relative to $Pd(OAc)_2$) in propionitrile at 100°C for 3 h furnishes the branched product in 88% yield with 98% regioselectivity. Other diphosphines such as dppp and dppb afford high branched-selectivity as well and other alkynes behave similarly. Very interestingly, near the same procedure using di(*o*-tolyl)phenylphosphine in place of dppe and toluene as the solvent induces dehydrogenative double addition leading to



R^1	R^2	conditions	yield (branched/linear)
Ph	Ph	60 °C, 3 h	99 (< 1/99)
n-Hex	Ph	90 °C, 12 h	75 (15/85)
Ph	$PhCH_2$	60 °C, 18 h	76 (< 1/99)
n-Hex	$PhCH_2$	90 °C, 18 h	86 (< 1/99)

Scheme 26 Cu-ethylenediamine-catalyzed hydrophosphinylation with *sec*-phosphine oxides

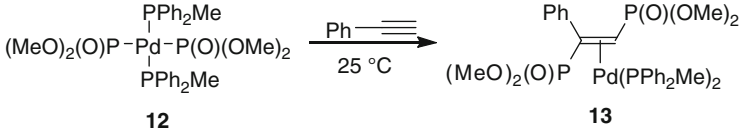


R	total yield (branched/linear)
p-Tol	90 (88/2)
n-Hex	82 (81/1)

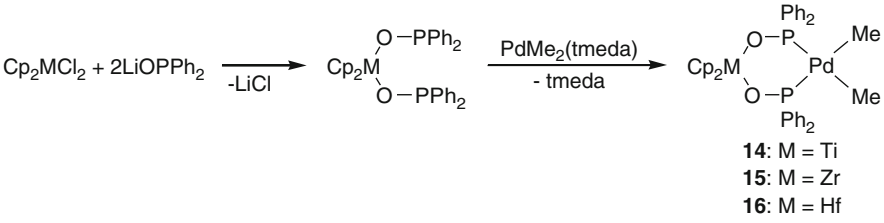
Scheme 27 Ligand-dependent reactivity in Pd-catalyzed addition of diphenylphosphine oxide across terminal alkynes

the formation of (*E*)-1,2-bis(diphenylphosphinyl)ethene derivatives as the major product. Addition of hydrogen acceptors can be beneficial to enhance the dehydrogenative double addition. The selective formation of the (*E*)-isomer is in good agreement with complex **12** being transformed to **13** upon treatment with 1 equiv. of phenylacetylene (Scheme 28) [34] (in view of *trans*-Pd[P(O)$(OMe)_2]_2(PPh_2Me)_2$ being generated upon treatment of *cis*-$Me_2Pd(PPh_2Me)_2$ with $HP(O)(OMe)_2$, an analogous species like *trans*-$[Ph_2P(O)]_2PdL_2$ can be involved in the present reaction; see [35]). However, the mechanism of the dehydrogenative double hydrophosphinylation and also the branched-directing nature of dppe remain to be further studied.

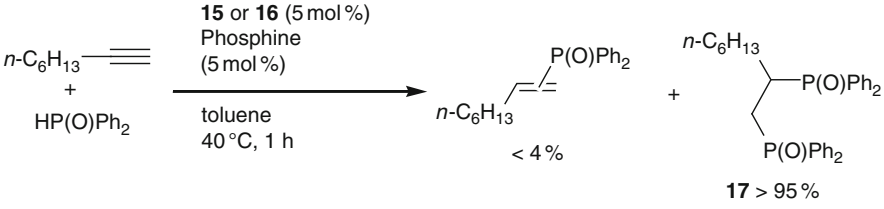
Mizuta and coworkers have synthesized early–late heterodinuclear transition metal complexes $Cp_2M(\mu\text{-}OPPh_2)_2PdMe_2$ (M=Ti (**14**), Zr (**15**), and Hf (**16**)) (Scheme 29) and found that **15** and **16** catalyze, highly efficiently when a phosphine ligand (PPh_2Me, $PPhMe_3$) is added, double addition of $HP(O)Ph_2$ to 1-octyne to mainly give 1,2-bis(diphenylphosphinyl)octane **17** in >95% yield under mild conditions (typically 5 mol% catalyst, 40°C, 1 h) (Scheme 30) [36]. The activity decreases in the order of Hf > Zr > Ti, which is partially associated with the



Scheme 28 Possible elemental process behind dehydrogenative double phosphinylation



Scheme 29 Preparation of early-late heterodinuclear complexes as precatalysts for double hydrophosphinylation of alkynes

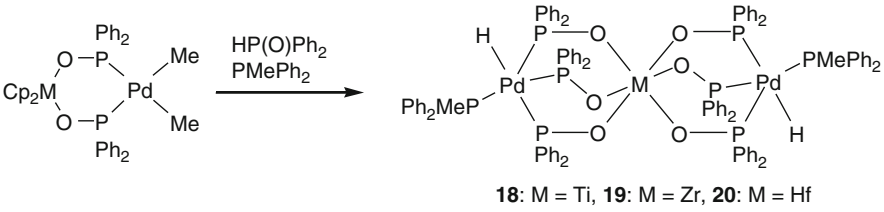


Scheme 30 Double hydrophosphinylation of alkynes using early-late heterodinuclear complexes as precatalysts

solubility of the catalyst. Irrespective of the catalyst and the conditions, the formation of the single addition product is very little.

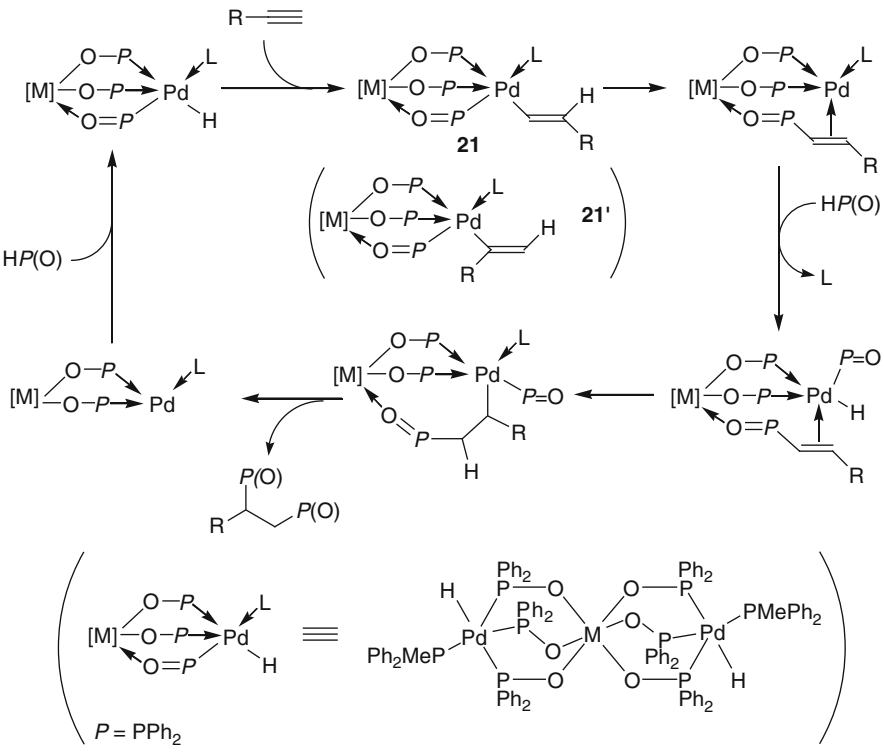
The beneficial role of the addition of a phosphine ligand is rationalized by the formation of trinuclear complexes **18**–**20** (Scheme 31), which are believed to be the real active species. The same trinuclear complexes are generated by simply mixing Cp_2MCl_2, $PdMe_2(tmeda)$, $HP(O)Ph_2$, and an appropriate phosphine, and the in situ-generated species have proved to catalyze the addition reaction as well.

The mechanism of the catalysis by the trinuclear species has been proposed as shown in Scheme 32. The first P–C bond forming process is basically the same as



18: M = Ti, **19**: M = Zr, **20**: M = Hf

Scheme 31 Generation of early-late trinuclear complexes, candidate active species

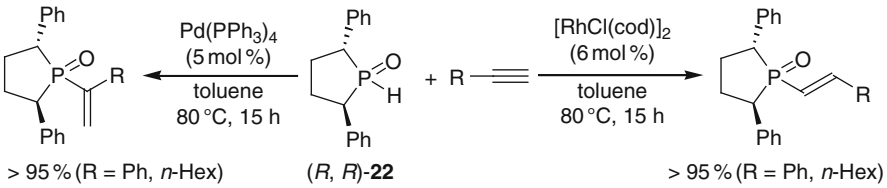


Scheme 32 Proposed mechanism of double hydrophosphinylation of alkynes

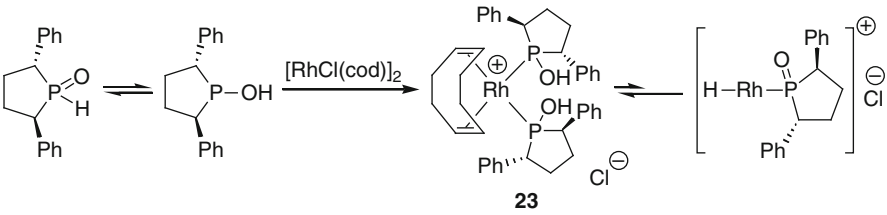
the well-known single addition process. In the mechanism, intermediate **21** after the hydropalladation process is proposed to have a linear alkenyl structure, and the subsequent species thereof are also formulated in line with this assumption. In view of the foregoing highly branched-selective addition displayed by the Pd-diphosphine (diphosphine = dppe, dppp, dppb) catalyst systems [17], however, branched alkenyl species like **21′** and relevant species that follow appear to deserve serious consideration. At this moment, the branched/linear ratio among the minor single addition products is not available to consider further. In any event, the intriguing role played by the group 4 metals lies in retaining the single addition product in the coordination sphere through its interaction with the oxygen in the O=P functionality, which allows the product to readily undergo the second addition of $HP(O)Ph_2$. The time course of the reaction followed by ^{31}P NMR spectroscopy has verified that the single addition product does not accumulate significantly throughout the reaction, but appears to react further as soon as it has been formed, which is somewhat different from the other double phosphinylation reactions [30, 31].

Toffano and coworkers applied the hydrophosphinylation of alkynes to the synthesis of chiral phosphines starting with chiral *trans*-2,5-diphenylphospholane oxide (*R*,*R*)-**22** (Scheme 33) [37]. The Pd-dppe catalyst system, highly branched-selective for hydrophosphinylation with diarylphosphine oxide [17], does not promote the reaction. However, use of $Pd(PPh_3)_4$ (toluene, 80°C, 15 h) affords branched adducts selectively in >95% yields from a variety of terminal alkynes, while $[Rh(cod)Cl]_2$ gives linear adducts preferentially.

Mixing $[Rh(cod)Cl]_2$ and (*R*,*R*)-**22** (2 equiv.) generates complex **23** immediately (related complexes have been isolated; see [38]) (the structure of the product may be dependent on the starting secondary phosphine oxide. For a related work, see [39]), which does not display a Rh-H signal in ^1H NMR spectroscopy (Scheme 34).



Scheme 33 Synthesis of chiral alkenylphospholane oxides via hydrophosphinylation of alkynes

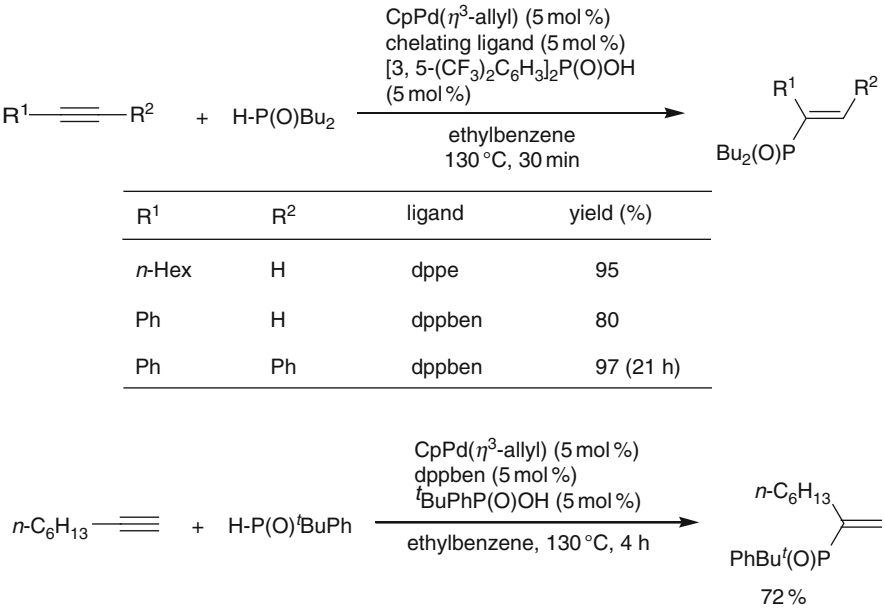


Scheme 34 Candidate species involved in Rh-catalyzed hydrophosphinylation with hydrophospholane oxide

However, addition of phenylacetylene to this complex displays new signals assignable to the linear product. Complex **23** is presumed to be in equilibrium with a hydride species, and the latter is likely to be a minor but very reactive component that carries the catalysis. Normal hydrorhodation followed by reductive elimination leads to the linear product.

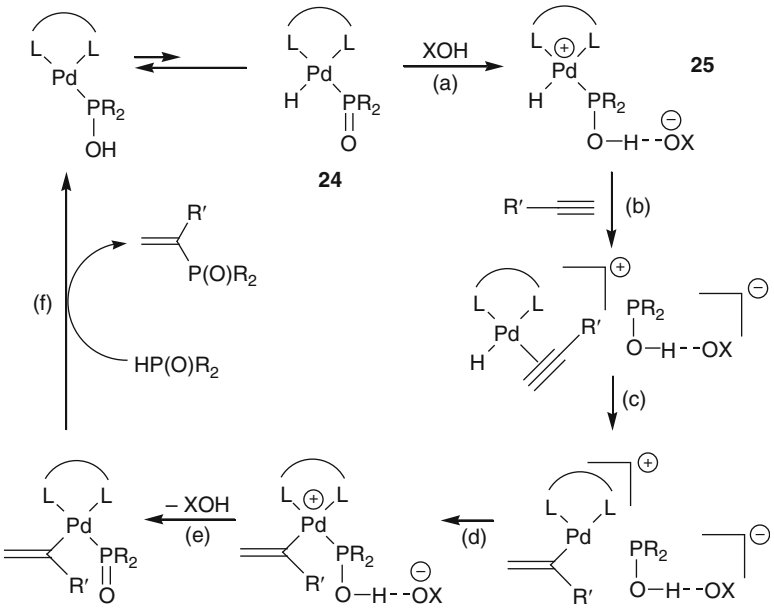
Despite extensive study on addition reactions of diarylphosphine oxides, HP(O)Ph_2 in particular, extension to dialkylphosphine oxides has been rather neglected and grown at a sluggish pace. However, a great advancement has been made recently using palladium and Brønsted acid in the presence of chelating phosphines [40–42]. Thus, addition reactions of $HP(O)Bu_2$ with a variety of terminal alkynes run at 130°C using dppe or dppben [dppben=1,2-bis(diphenylphosphino)benzene] as ligand and $[3,5\text{-}(CF_3)_2C_6H_3]_2P(O)OH$ as Brønsted acid complete in 30 min to mainly afford branched isomers in good yields (Scheme 35). Diphenylacetylene also gives the corresponding adduct in 97% yield although completion requires 21 h. HP(O)Ph^{t}Bu, a bulky alkylarylphosphine oxide, also adds to 1-octyne in the presence of Ph^{t}BuP(O)OH as acid to achieve 72% (130°C, 4 h) of the corresponding branched adduct.

A mechanism that involves a zwitterionic intermediate **25** that is featured by hydrogen bonding interaction between its $P(O)R_2$ moiety and a Brønsted acid (X-OH) is proposed (Scheme 36). Formation of such a complex has not been substantiated with palladium due to the difficulty of isolation of species **24**. However, platinum analogues $HPt[P(O)R_2](dmpe)$ have been found to react

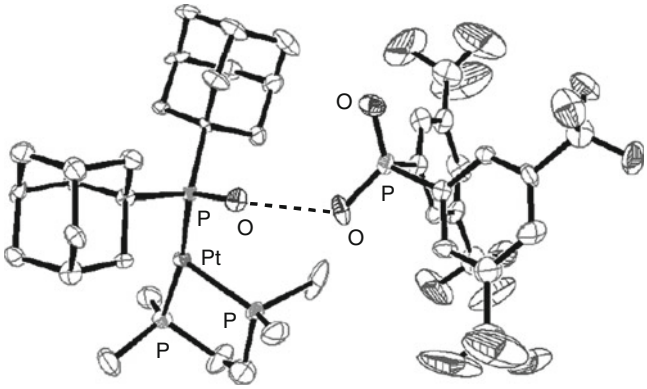


R^1	R^2	ligand	yield (%)
n-Hex	H	dppe	95
Ph	H	dppben	80
Ph	Ph	dppben	97 (21 h)

Scheme 35 Pd-Brønsted acid-catalyzed hydrophosphinylation with alkylphosphine oxide



Scheme 36 Proposed mechanism of Pd-Brønsted acid-catalyzed hydrophosphinylation



Scheme 37 X-ray crystal structure of zwitterionic intermediate

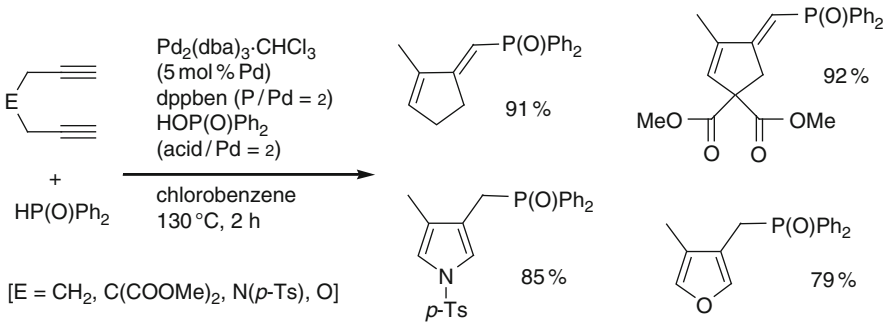
with a series of diarylphosphinic acids to generate similar zwitterionic species displaying hydrogen bonding interaction. Treatment of $HPt[P(O)Ad_2](dmpe)$ (Ad = adamantyl) having a more basic dialkylphosphinyl ligand, $P(O)Ad_2$, with strongly acidic $[3,5\text{-}(CF_3)_2C_6H_3]_2P(O)OH$ (1.0 equiv.) allowed isolation of a zwitterionic complex similar to species **25**, the structure of which was confirmed by X-ray analysis (Scheme 37). Its phosphine-like $PAd_2[OH\cdots OP(O)(3,5\text{-}(CF_3)_2C_6H_3)_2]$ is coordinatively labile to readily undergo ligand exchange with *t*-BuNC, while

neutral HPt[P(O)Ad_2](dmpe) is totally unreactive. The more protonic nature of the cationic "hydridopalladium" moiety is envisioned to direct the reaction in favor of Markovnikov addition (branched-selective). A mechanism involving phosphopalladation has been proposed for the reaction of terminal alkynes with HP(O)Ph_2 using the palladium-Ph_2P(O)OH catalyst system [9]. On the basis of the new findings, however, the mechanism, the role of Ph_2P(O)OH in particular deserves further detailed study.

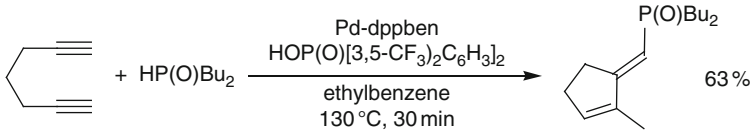
The addition-cyclization reaction of HP(O) compounds catalyzed by palladium-diphosphine catalyst systems [22] proceeds more selectively by the addition of Brønsted acids. For instance, the Ph_2P(O)OH-assisted reaction of 1,6-heptadiyne or analogues with HP(O)Ph_2 affords the cyclized products in high yields (Scheme 38) [40]. A similar cyclization reaction with HP(O)Bu_2 also proceeds in an acceptable yield (Scheme 39) [41].

The favorable effect of a Brønsted acid on the addition reaction of HP(O) compounds is also seen in the nickel–diphosphine complex-catalyzed addition of dibutylphosphine oxide to give the branched product as near the sole product (Scheme 40) [43].

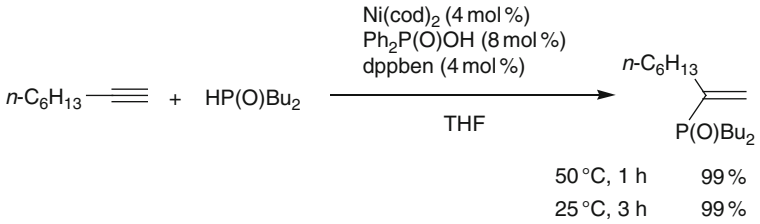
An oxaphosphapalladacycle **26**, which is obtained by the treatment of Pd(OAc)$_2$ with Ph_2P(O)OH (1.5 equiv.) in THF at 60°C, has proved to catalyze, in combination with dppe or dppp, high-yielding and branched-selective addition of various H–P(O) compounds, inclusive of somewhat less reactive HP(O)Me_2 (Schemes 41 and 42) [44].



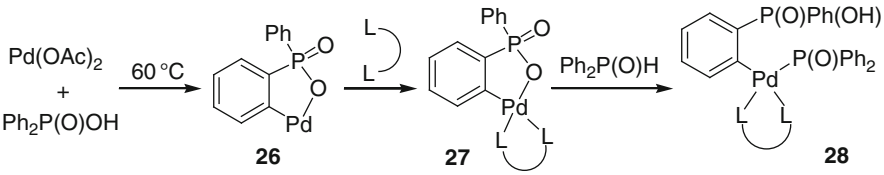
Scheme 38 Enhanced catalytic activity in hydrophosphinylative carbocyclization boosted by Brønsted acid



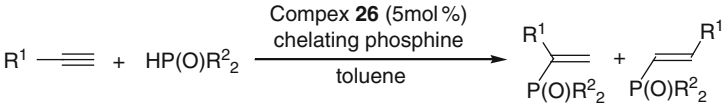
Scheme 39 Hydrophosphinylative carbocyclization with dibutylphosphine oxide



Scheme 40 Highly efficient Ni-catalyzed hydrophosphinylation of alkynes with dibutylphosphine oxide



Scheme 41 Generation of candidate active species from $Pd(OAc)_2$ and $Ph_2P(O)OH$

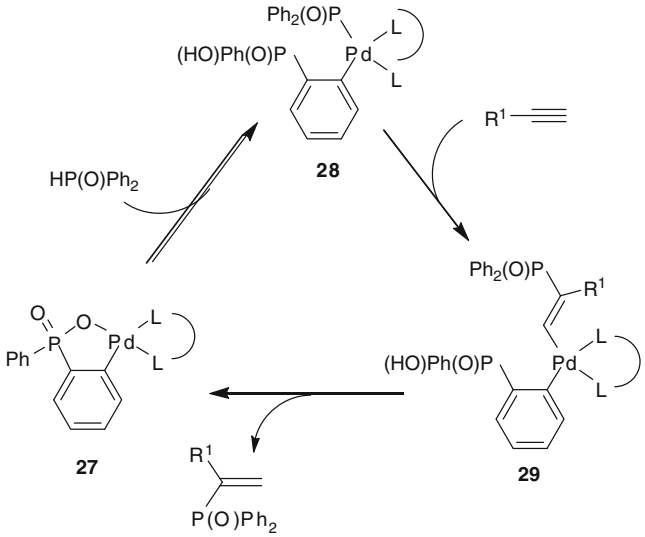


R^1	R^2	ligand	conditions	yield(%)	branched / linear
n-Hex	Ph	dppp	70 °C, 3 h	99	98 / 2
tert-Bu	Ph	dppe	70 °C, 10 h	97	99 / 1
Ph	Ph	dppp	70 °C, 20 h	99	—
n-Hex	Me	dppp	110 °C, 5 h	99	98 / 2
tert-Bu	Me	dppe	110 °C, 25 h	96	95 / 5

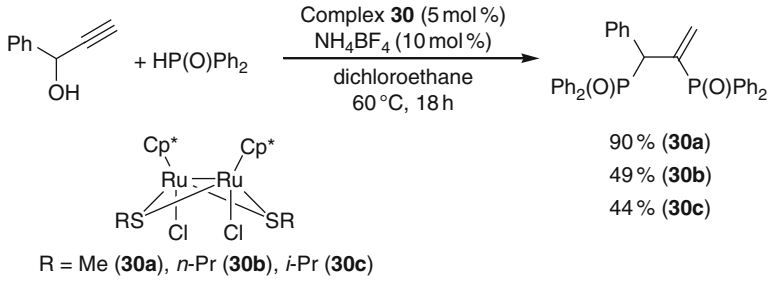
Scheme 42 Hydrophosphinylation of terminal alkynes in the presence of hexamer of complex **26**

Complex **26** forms a D_3 symmetric hexamer in crystalline state, which reacts with dmpe or dppe (1.0 equiv. relative to Pd) to degrade the hexamer aggregate to give monomeric complex **27** ligated by the chelating phosphine (Scheme 41). Complex **27-dmpe** reacts with $HP(O)Ph_2$ to be transformed to complex **28-dmpe**, as confirmed by X-ray analysis. Upon heating, a solution of complex **27-dppe** (0.015 mmol), $HP(O)Ph_2$ (0.1 mmol), and 1-octyne (0.11 mmol) at 70°C overnight gives the branched adduct (99% yield) in addition to **27-dppe** recovered. On the basis of these experiments, a mechanism shown in Scheme 43 has been proposed. Although phosphopalladation is proposed, intermediate **29** has not been confirmed in the experiment.

Besides exploration for new catalysts and new mechanistic possibilities, application of the hydrophosphinylation to synthesize more practically useful phosphorus



Scheme 43 Proposed mechanism of hydrophosphinylation of terminal alkynes in the presence of hexamer of complex **26**



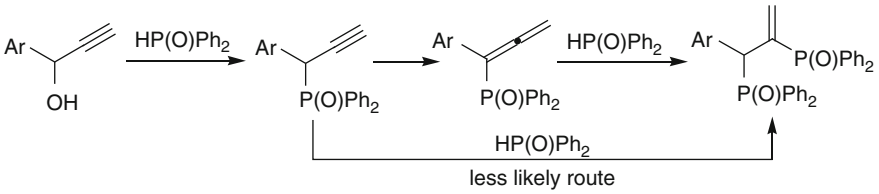
Scheme 44 Ru-catalyzed reaction of propargylic alcohol with diphenylphosphine oxide

compounds is another direction of the research. Among these, propargyl alcohols have attracted special attention.

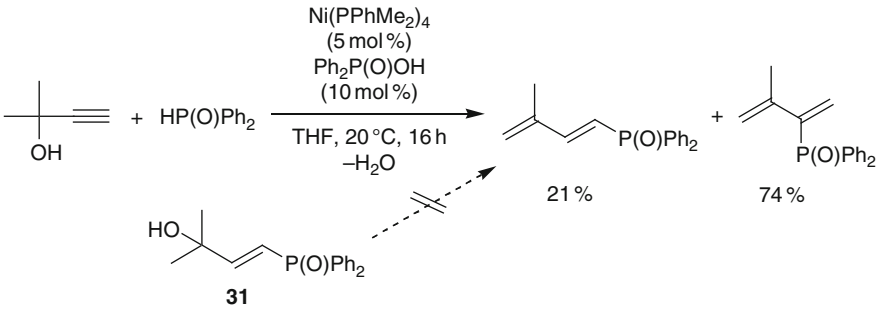
The reaction of 1-aryl-2-propynols (propargylic alcohols) with $HP(O)Ph_2$ in the presence of dinuclear ruthenium complexes **30** produces 2,3-bis(diphenylphosphino)propene derivatives in high yields (Scheme 44) [45].

Propargylic substitution forming propargyldiphenylphosphine oxide [46] is likely to be the first process, which is followed by isomerization to allenylphosphine oxide and branched-selective addition of a second $HP(O)Ph_2$ (Scheme 45). Direct addition to the propargyldiphenylphosphine oxide is less likely since allenylphosphine oxides can be isolated and other simple alkynes such as 1-hexyne and phenylacetylene are inert toward hydrophosphinylation.

The reaction of propargyl alcohols, when run using a nickel–phosphine complex catalyst at room temperature, affords linear products **31** as is well known for



Scheme 45 Possible pathway involved in Ru-catalyzed reaction of propargylic alcohol with diphenylphosphine oxide

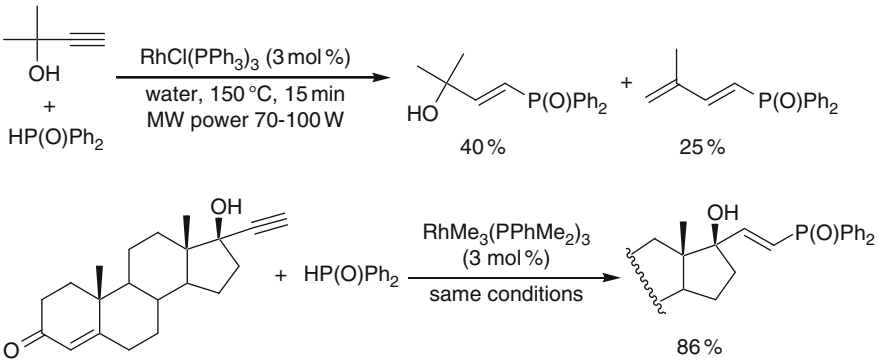


Scheme 46 Ni-$Ph_2P(O)OH$-catalyzed dehydrative addition of diphenylphosphine oxide with propargylic alcohol

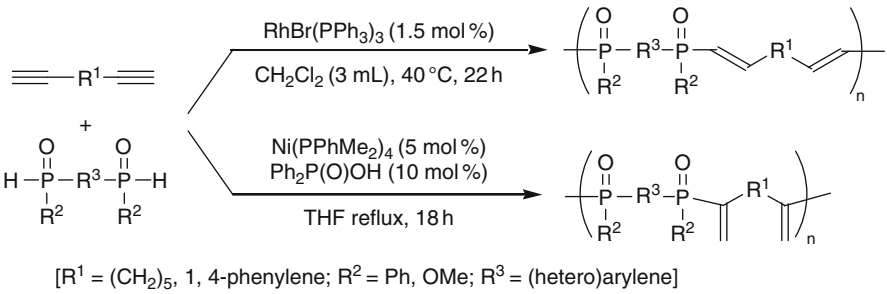
terminal alkynes. The products can be dehydrated by heating with H_2SO_4 (e.g., at 70°C, 20 min, 88%). However, using the same nickel–phosphine complex in the presence of diphenylphosphinic acid, the addition and dehydration proceed in a single step to give an isomeric mixture of phosphinylated butadiene derivatives even at room temperature (Scheme 46) [47]. Since the linear compound **31** does not undergo dehydration under the diphenylphosphinic acid-assisted conditions, the formation of the butadiene derivatives via dehydration of **31** is not a likely pathway. Another sequence comprising dehydration and subsequent addition of $HP(O)Ph_2$ to the resulting enyne compound may be a real route. Besides $HP(O)Ph_2$, $HP(O)(OMe)_2$ and HP(O)Ph(OEt) also furnish regioisomeric mixtures of butadiene derivatives in moderate yields.

Similar dehydrative addition of HP(O) compounds also proceeds with rhodium catalysts. Thus, the reaction of $Ph_2P(O)H$ or *H*-phosphinates with propargyl alcohols using $(Ph_3P)_3RhCl$, $[Rh(cod)Cl]_2$, or $(Me_2PhP)_3RhMe_3$ for 15 min at 150°C under microwave irradiation affords corresponding adducts and relevant dehydration products (Scheme 47) [48]. Both products are linear-structured. Unlike simple propargyl alcohols, steroidal propargy1 alcohols undergo addition with $Ph_2P(O)H$ and other HP(O) compounds without extensive dehydration.

As another direction of applications, phosphorus-containing polymers ($M_n = 1.0–7.2 \times 10^4$, polydispersity = 1.4–2.4) are synthesized using the known procedures to the combinations of bis[HP(O)] compounds and α,ω-diynes (Scheme 48) [49].



Scheme 47 Rh-catalyzed microwave-assisted reaction of propargylic alcohol with diphenylphosphine oxide

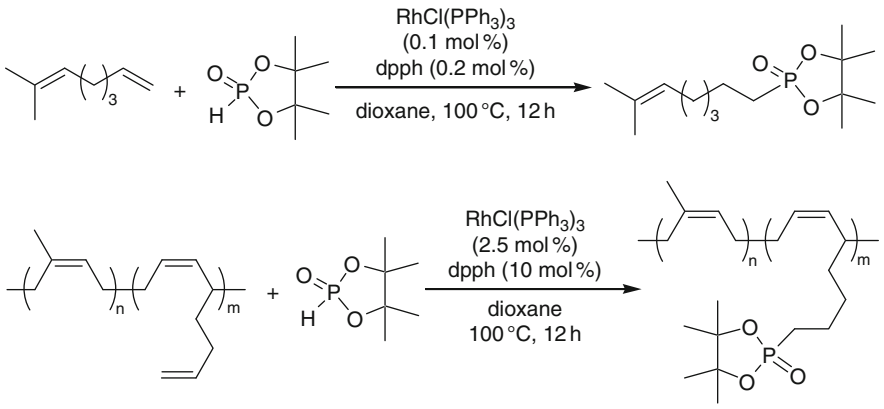


Scheme 48 A synthetic application of hydrophosphinylation to polymer synthesis

5 Addition Reactions of H–P(O) Compounds with Alkenes, Dienes, and Isocyanides

Addition to olefins has not made an epoch-making progress since the publications on hydrophosphorylation using pinacol phosphonate [50] and unsubstituted phosphinic acid (hypophosphorous acid) derivatives [25], inclusive of the extension to rhodium-catalyzed reactions of pinacol phosphonate [51]. No publication has appeared to disclose addition reactions of a phosphine oxide except for cyclopropenes (vide infra).

The rhodium-catalyzed addition of pinacol phosphonate has been revisited, focusing on the effect of the ligands using nonconjugated terminal-internal dienes [52]. Only the terminal double bond participates in the reaction to furnish linear products. At high substrate-to-rhodium ratios, e.g., $\geq$400, the catalytic activity diminishes gradually, which is associated with the oxidative deterioration of the phosphine ligand (PPh_3, PCy_3). Addition of a large quantity of the phosphine ligand improves the catalyst life and allows full conversion. Among the ligands screened, dpph [1,6-bis(diphenylphosphino)hexane] displays high performance as far as

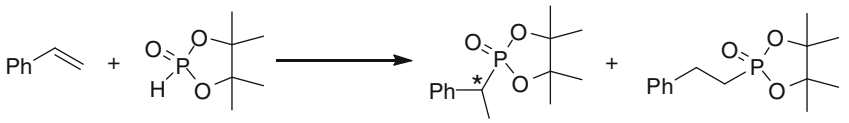


Scheme 49 Rh-catalyzed hydrophosphorylation of monomeric and polymeric non-conjugated dienes with pinacol phosphonate

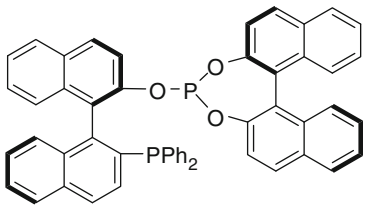
dioxane solvent is concerned and allows the yield, TOF and TON up to 96%, 250 h^{-1} and 4,550, respectively (Scheme 49). The optimized recipe can be applied readily to introduce phosphoryl groups to a polymer to produce functional elastomers starting with poly(isoprene-*co*-1,3,7-octatriene) copolymers [53].

Since palladium-catalyzed hydrophosphorylation of styrene with pinacol phosphonate is exceptionally branched-selective, its asymmetric version has attracted a special interest (Scheme 50) [54–56]. Among the ligands screened, BINAPHOS **32** used in conjunction with CpPd(η^3-allyl) displays better performance (branched/linear = 93/7, 56% ee). The stereoselectivity can be boosted to 74% ee by the introduction of a trifluoromethanesulfonyl group to the ligand like **33** although the branched/linear ratio decreases to 76/24. Use of a Josiphos family ligand **34** and $Pd(OAc)_2$ shows similar stereoselectivity (73% ee) and a higher branched/linear ratio (>94/6) at a lower temperature. Asymmetric hydrophosphorylation of norbornene also affords a high stereoselectivity (89% ee) under optimized conditions using $Pd(OAc)_2$ and another Josiphos-type ligand **35** in the presence of NEt_3 as an additive although the reaction is quite slow (Scheme 51). Microwave irradiation accelerates the reaction, but does not improve the stereoselectivity.

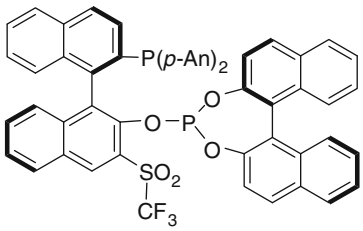
Cyclopropenes participate successfully in the addition reaction with various HP(O) compounds under mild conditions [57]. Catalyst screening using pinacol phosphonate and 3-methyl-3-phenylcyclopropene has revealed that $Pd(PPh_3)_4$ and Pd_2dba_3/dppf appear the catalysts of choice giving the isomeric mixture of the desired adducts **36**, mainly comprising the *trans*-adduct, in high yields, while other catalysts are less active and/or less selective and can form a side product, allylphosphonate **37** (Scheme 52) more extensively. Functionalized cyclopropenes also react successfully. Furthermore, even diphenylphosphine oxide undergoes addition to cyclopropenes, providing one of the first examples of successful addition of a *sec*-phosphine oxide with an alkene (Scheme 53).



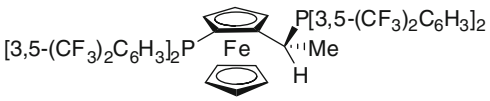
catalyst	ligand	conditions	% ee	branched/linear
CpPd(η^3-allyl) (5 mol %)	**32** (5 mol %)	100 °C, 12 h	56	93/7
[Pd(η^3-allyl)(MeCN)$_2$]OTf + NaCH(CO$_2$Me)$_2$ (5 mol %)	**33** (5 mol %)	100 °C, 18 h	74	76/24
Pd(OAc)$_2$ (5 mol %)	**34** (7.5 mol %)	80 °C, 90 h	73	94/6



(*R*,*S*)-BINAPHOS **32**

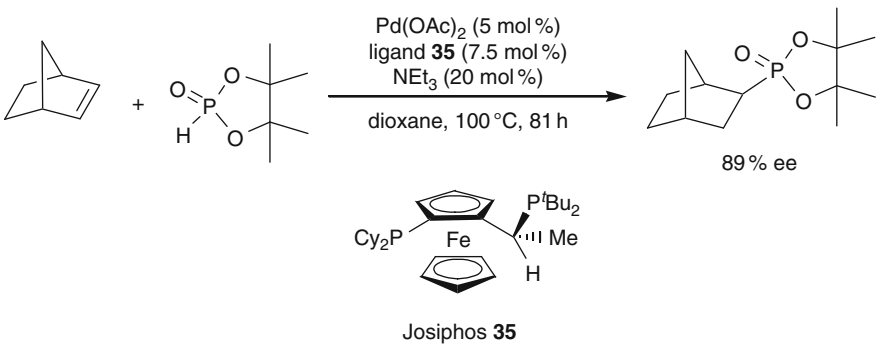


3'-Sulfonyl (*R*,*S*)-BINAPHOS **33**



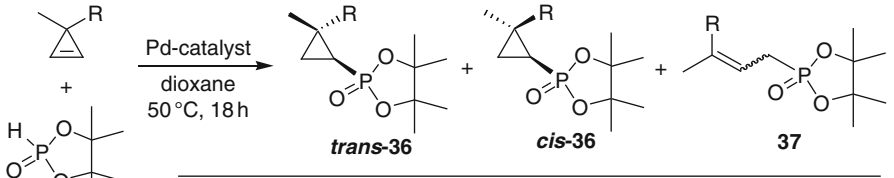
Josiphos **34**

Scheme 50 Asymmetric hydrophosphorylation of styrene with pinacol phosphonate



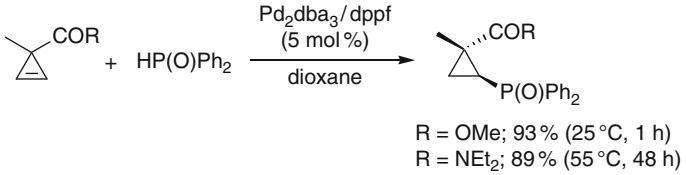
Scheme 51 Asymmetric hydrophosphorylation of norbornene with pinacol phosphonate

A mechanism similar to those well established has been proposed (Scheme 54). An experiment using 1,2-dideuterio-3-methyl-3-phenylcyclopropene verifies stereospecific *cis*-addition having taken place. The formation of allylphosphonate

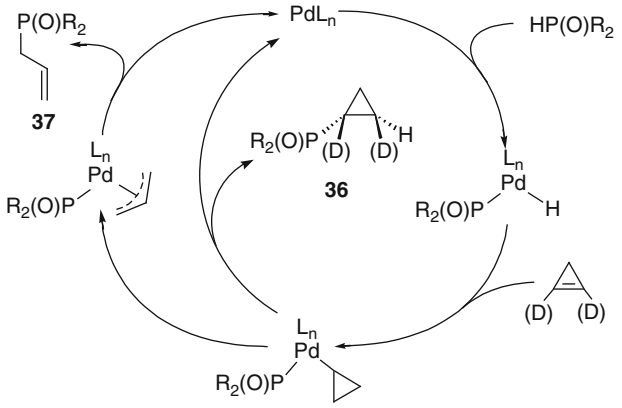


R	catalyst	**36** yield(%) (*trans*/*cis*)	**37** yield(%)
Ph	$Pd(PPh_3)_4$	89 (19/1)	6
COOMe	Pd_2dba_3/dppf	97 (9/1)	0

Scheme 52 Hydrophosphorylation of cyclopropenes



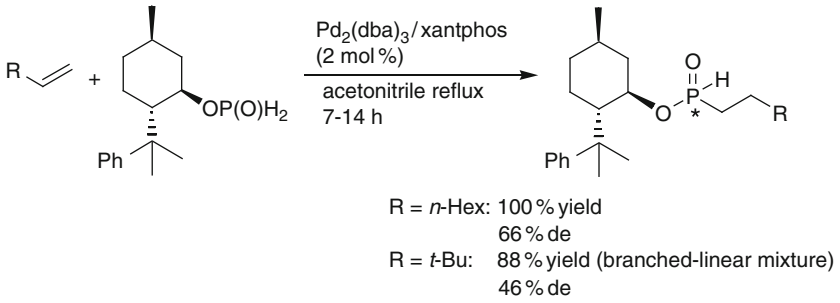
Scheme 53 Hydrophosphinylation of cyclopropenes



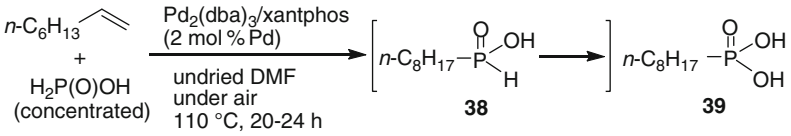
Scheme 54 Mechanism of hydrophosphorylation of cyclopropene

37 is rationalized by β-carbon elimination generating η^3-allylpalladium species [58], followed by P–C reductive elimination thereof.

Palladium complexes like Pd/xantphos are known to efficiently catalyze addition of alkyl phosphinates to terminal olefins to give linear adducts as the major products [25]. When the reaction of (−)-8-phenylmenthyl phosphinate with olefins is run using the Pd/xantphos catalyst, enantioselective addition proceeds to give diastereomeric mixtures of *P*-chiral (−)-8-phenylmenthyl alkylphosphinates (Scheme 55). Stereoselectivities up to 66% and 71% de are observed for 1-octene



Scheme 55 Enantioselective addition of chiral dihydrophosphinate with terminal alkenes



Remarks	**38** (%)	**39** (%)
(standard conditions)	0	74
2 equiv of $H_2P(O)OH$ used	0	100
anhydrous DMF,under N_2	82	10
catalyst loading: 0.05 mol % 2 equiv of $H_2P(O)OH$ used	100	0

Scheme 56 Pd-catalyzed addition of hypophosphorous acid with terminal alkenes under air

and 2-bromostyrene, respectively [59]. Phosphinates having other chiral alkoxy groups are inferior. Asymmetric hydrophosphinylation of 1-octene with ethyl phosphinate in the presence of a series of chiral ligand–palladium catalyst systems affords only marginal stereoselectivities.

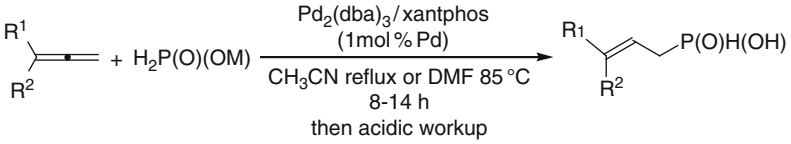
A modified procedure of the addition of unsubstituted phosphinic acid (hypophosphorous acid) has realized a one-pot synthesis of alkylphosphonic acids [60]. Alkylphosphinic acids [(alkyl)HP(O)OH] resulting from the addition of phosphinic acid is known to be readily oxidized to form corresponding alkylphosphonic acids, which are useful in diverse applications. In the modified procedure, reactions are run under air to in situ oxidize the initially formed alkylphosphinic acids, using Pd_2dba_3 (1 mol%) and xantphos (2 mol%) at 110°C (Scheme 56). Undried reagent grade DMF has proved to be a convenient reaction medium. The reaction of 1-octene under the conditions affords *n*-octylphosphonic acid **39** selectively, while another reaction under nitrogen in anhydrous DMF is reluctant to oxidize *n*-octylphosphinic acid **38**, which is obtained as the major product (82% yield). When a smaller quantity of the catalyst is loaded (0.05 mol%) using undried DMF solvent, the phosphinic acid is obtained quantitatively even under air, suggesting that palladium species is participating in the oxidation process.

Other alkenes inclusive of functionalized ones and also an alkyne (4-octyne) conform to the new procedure successfully. The reaction mechanism under air is not clear. It may involve initial activation of molecular oxygen to generate highly reactive radical species.

Allenes and dienes also react with phosphinic acid or its anilinium salt, typically in the presence of $Pd_2(dba)_3$/xantphos (1 mol%) at 110°C (Scheme 57) [61]. Acetonitrile and DMF are the solvents of choice for phosphinic acid and DMF for the anilinium salt. 3,3-Disubstituted allenes and phenylallene react with phosphinic acid regioselectively and with a high *E*-selectivity to furnish allylic *H*-phosphinic acids in moderate to high yields. On the other hand, the regio- and stereoselectivities observed for 3-alkylallenes are low, but can be significantly improved using the anilinium salt.

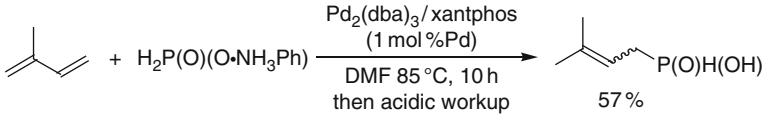
Unlike allenes, conjugated dienes are inert toward hydrophosphinylation except for isoprene and its analogues (Scheme 58). Nonconjugated α,ω-dienes react selectively at one of the terminal C=C bonds forming a linear product. Enyne compounds react at the C≡C bond selectively although they furnish unselective mixtures of regio- and stereoisomers.

As already mentioned (Sect. 2), $Mo(CO)_6$ catalyzes hydrophosphorylation of phenylacetylene [19]. Similar addition reaction of *H*-phosphonates to cyclohexene proceeds when a mixture of cyclohexene (4 equiv.), $HP(O)(OR)_2$ (R=Me, Et, ^{i}Pr), metal carbonyl (10 mol%; $Fe(CO)_5$, $W(CO)_6$, $Mo(CO)_6$ or $Cr(CO)_6$), and a catalytic quantity of triethylamine is refluxed for 5 h under argon (Scheme 59) [62]. The yield is low (<30%). Treatment of $Fe(CO)_5$ or $W(CO)_6$ with $HP(O)(OEt)_2$ appears to generate M-P(O)$(OEt)_2$ species (M=Fe, W), on the basis of ^{31}P NMR spectroscopy, which displays, for M=W, a satellite band possibly arising from coupling

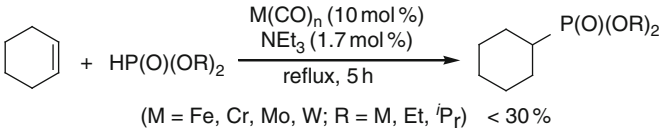


R^1, R^2	M	solvent	yield(%)
$R^1 + R^2 = -(CH_2)_5-$	$M = PhNH_3$	DMF	64 %
R^1 = Ph, R^2 = H	$M = PhNH_3$	DMF	98 %
	M = H	CH_3CN	100 %

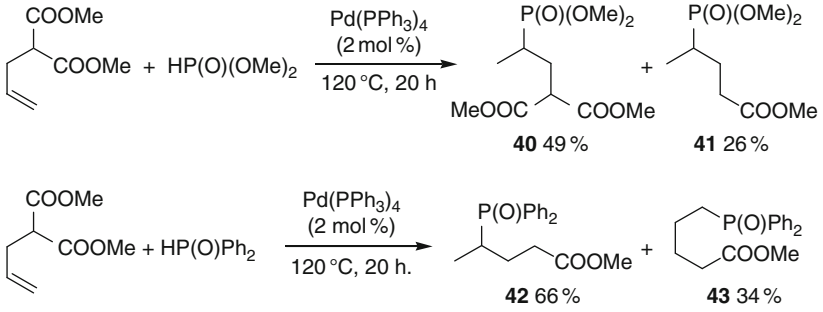
Scheme 57 Hydrophosphorylation of allenes with dihydrophosphinic acid derivatives



Scheme 58 Hydrophosphorylation of isoprene with anilinium dihydrophosphinate



Scheme 59 Matal carbonyl-catalyzed hydrophosphorylation of cyclohexene

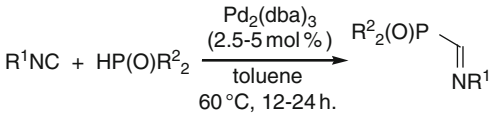


Scheme 60 Addition reaction of dimethyl phosphonate or diphenylphosphine oxide with allylmalonate

between ^{183}W and ^{31}P nuclei ($J = 353$ Hz). Furthermore, treatment of the tungsten complex with cyclohexene and $HP(O)(OEt)_2$ triggers a vigorously exothermic reaction affording diethyl cyclohexylphosphonate in 80% yield. However, the structure of these complexes has not been characterized further and mechanistic details remain to be clarified.

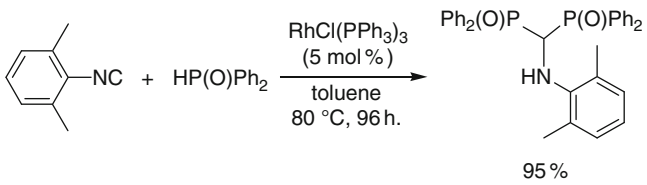
The reactions of 2-allylmalonates with various HP(O) compounds disclosed by Reznikov and Skvortsov (Scheme 60) are quite amazing [63], in view of the lack of reactivity of olefinic bonds toward *H*-phosphonates except pinacol phosphonate [50]. In the presence of $Pd(PPh_3)_4$ (2 mol%), dimethyl 2-allylmalonate reacts with $HP(O)(OMe)_2$ at 120°C for 20 h to produce the branched adduct **40** and the demethoxycarbonylation product of the branched structure **41** in 49% and 26% yields, respectively (since the total yield is not reported, the yield is calculated on the basis of the conversion of the phosphonate and the selectivity). Diphenylphosphine oxide also reacts under similar conditions, but the major product was branched demethoxycarbonylation product **42** in 66% yield together with linear demethoxycarbonylation product **43** in 34% yield. This reaction provides another successful example of addition of a *sec*-phosphine oxide to alkenes.

Isocyanides have proved to react with *sec*-phosphine oxides to give 1,1- and/or 1:2 adducts in good yields [64]. For instance, a toluene solution of $2,6\text{-}Me_2C_6H_3NC$ and $Ph_2P(O)H$ (1 equiv.) gives, after heating at 60°C for 24 h in the presence of $Pd_2(dba)_3$ (5 mol%), the corresponding 1:1 adduct in 99% yield together with a trace of 1:2 adduct (Scheme 61). Alkylarylphosphine oxide and dialkylphosphine oxide also participate in the reaction similarly. Other palladium(0) complexes ligated by phosphines catalyze the addition as well, while Pd(II) species, Ni $(cod)_2$, $Ni(cod)_2/4PPh_3$, and $[Pt(PPh_3)_2(CH_2{=}CH_2)]$ display only a weak or no



R^1	R^2	yield (%)
2, 6-$Me_2C_6H_3$	Ph	99
Cy	Ph	90
t-$BuCH_2$	Ph	74
2, 6-$Me_2C_6H_3$	Me	43
2, 6-$Me_2C_6H_3$	*n*-Bu	81

Scheme 61 Palladium-catalyzed 1,1-addition between *sec*-phosphine oxides and isocyanides



Scheme 62 Rhodium-catalyzed 2:1-adduct formation from diphenylphosphine oxide and 2,6-dimethylphenylisocyanide

activity. Unlike the palladium-catalyzed reactions, the 1:2 adduct can be obtained as the major product when the reaction is effected at 80°C over 4 days using rhodium catalysts (5 mol%) such as $Rh(PPh_3)_3Cl$ (95%), $Rh(PPh_3)_3Br$ (88%), $Rh(PPh_3)_3I$ (69%), and $[Rh(cod)Cl]_2$ (94%) (Scheme 62). Apparently, the second addition of $Ph_2P(O)H$ forming 1:2 adduct is promoted by rhodium but not by palladium. $Bu_2P(O)H$ is near unreactive in the rhodium-catalyzed reaction under similar conditions. The reaction using the palladium catalysts is rationalized by an intermediate like (iminoformyl)(phosphinyl)palladium species generated by insertion of isocyanide into H–Pd bond. However, convincing evidence has not been provided.

6 Conclusion and Future Prospects

After 15 years have passed since the first publication on the metal complex-catalyzed addition of *H*-phosphonate, almost all possible variations in the H–P(O) bond addition reactions have already been published. After the overview of the progress since some 8 years ago herein summarized, the remaining area for future research has become clear and can be summarized as follows:

1. *Search for more ubiquitous metal catalysts for the transformation*: Although nickel catalysts have been used quite successfully depending on the structure of the H–P(O) compounds, the coverage is still rather limited. Also, nickel is still near the only one non-noble metal that is active for the transformation. The successful progress in cross-coupling chemistry provides a good example, which shows the direction of the research toward the use of more ubiquitous metals. There is no reason why H–P(O) bond addition cannot be a next example.
2. *Mechanistic understanding*: A central question lies in the insertion process, which can proceed by either hydrometalation or phosphometalation. Although theoretical study has boosted our understanding, mechanistic proposals are not always substantiated by experiments. Also, P–C reductive elimination, which can be rate-determining, has not been well studied either. Why is only pinacol phosphonate, among dialkyl phosphonates, reactive toward the addition to alkenes? Why unsubstituted phosphinic acid and its derivatives are also reactive toward the addition to alkenes? These questions await our answers to expand the scope of the addition reaction.
3. *How to control the regioselectivity*: In most of the H–P(O) bond addition reactions to terminal alkynes and alkenes, the branched products are more valuable since the linear products can be synthesized by classical radical processes. Some of the metal-catalyzed processes are branched-selective or allow regiochemical flexibility by tuning the procedure. In view of problematic separation of the isomers, however, we still have a long way to go before we perfect the regiochemical control for practical use.

While these tasks are being successfully accomplished, we have more opportunities in asymmetric additions, wide-ranging use of the products in the synthesis of practically important phosphorous compounds, and further extension of the reaction concept from H–P(O) to heteroatom-P(O) bonds.

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Group 8 Metals-Catalyzed O–H Bond Addition to Unsaturated Molecules

Christian Bruneau

Abstract The formation of carbon–oxygen bond upon addition of *O*-nucleophiles to unsaturated molecules is very attractive as it represents an atom economical strategy to prepare a variety of saturated compounds from olefins and vinylic derivatives from alkynes. Group 8 metals, especially ruthenium have provided an important contribution in this field. We report here on iron- and ruthenium-catalyzed addition of nucleophiles to unsaturated systems. As additions to alkenes are still scarce with these metals and the use of iron catalysts is limited, the main part of the chapter is dedicated to addition of carbamates, carboxylic acids, alcohols and water to triple bonds with ruthenium catalysts.

Keywords *Anti*-Markovnikov addition · Enol esters · Hydration · Nucleophilic addition · Ruthenium catalysis · Unsaturated cyclic ethers · Vinyl carbamates

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1 Introduction

Modern chemistry requires synthetic methods able to perform transformations with high efficiencies and selectivities. For cost and environment issues, these processes have also to be as clean as possible and must therefore offer the possibility of performing transformations with atom economy. Catalytic reactions promoted by transition metal complexes are able to fulfil these characteristics. Among the group 8 transition metals, ruthenium catalysts have attracted much attention during the last 25 years. Indeed, due to their high versatility, ruthenium catalysts can promote carbon–carbon or carbon–heteroatom bond formation via a wide range of mechanistic processes including carbon–carbon multiple bond activation. After a long period when they were mainly used as Lewis acid catalysts, iron catalysts are now in a phase of intense development and a few examples in the field of addition of nucleophiles to unsaturated C–C bonds have recently appeared. As far as osmium is concerned, the creation of C–O bonds mostly involves oxidation mechanisms with the use of oxidant such as *N*-methylmorpholine oxide for classical dihydroxylation for instance.

The main part of this chapter we will be devoted to ruthenium-catalyzed additions of *O*-nucleophiles to alkynes, including carbamates, carboxylic acids, alcohols and water. Ruthenium-catalyzed nucleophilic additions to alkynes are possible via different activation pathways with respect to the alkyne (Scheme 1). Several ruthenium complexes are able to promote the addition of *O*-nucleophiles to alkynes via Lewis acid-type activation of triple bonds leading to Markovnikov addition. Starting from terminal alkynes, the *anti*-Markovnikov addition to form vinyl derivatives is less common and requires selected catalysts. This regioselectivity corresponding to the addition of the nucleophile at the less substituted carbon of the carbon–carbon triple bond is expected to result from the formation of a ruthenium vinylidene intermediate featuring a highly reactive electrophilic Cα atom. This mechanism was first considered in 1986 to rationalize the formation of vinyl carbamates. Examples of nucleophilic addition of *O*-nucleophiles to alkenes in the presence of ruthenium and iron catalysts, even though they are not very common, will also be included in this review.

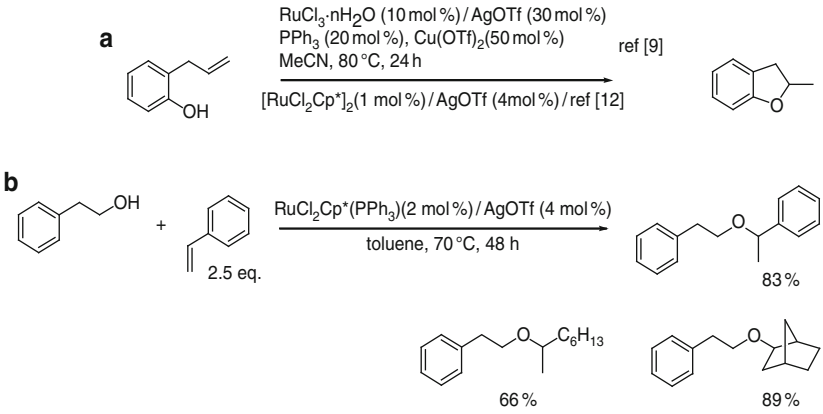
It is noteworthy that reviews covering or including carbon–oxygen bond formation via metal-catalyzed additions to unsaturated molecules and involving a wide range of metals have appeared during the last decade [1–8].

2 Addition to Olefins

2.1 Addition of Alcohols

Very few reports on group 8 metal-catalyzed addition of nucleophiles to carbon–carbon double bonds exist. The first example with the hydroxy functionality was probably the cyclization of 2-allylphenol, which regioselectively leads to the

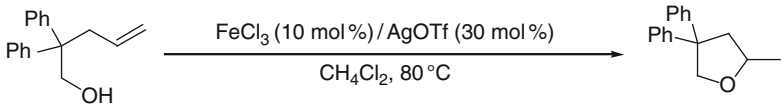
formation of 2-methylbenzodihydrofuran [9]. The catalytic system was based on the association of several metal salts (ruthenium chloride, silver and copper triflate) in the presence of triphenylphosphine and operated under mild conditions (80°C) (Scheme 1a). The exact nature of the catalytic species was difficult to determine as it was shown later that triflic acid [10, 11] and copper triflate [11] alone were also efficient hydroalkoxylation catalysts. A combination of $[RuCl_2Cp^*]_2$/AgOTf/phosphine also performed the same cyclization [12]. The intermolecular addition of 2-phenylethanol to styrene was investigated in details with $[RuCl_2Cp^*]_2$ and $RuCl_2Cp^*(PPh_3)$ as catalyst precursors. The most efficient system was based on $RuCl_2Cp^*(PPh_3)$ in the presence of AgOTf at 70°C in toluene and regioselectively led to the formation of the branched Markovnikov hydroalkoxylation product [13] (Scheme 1b). This catalytic system also made possible the regioselective addition of 2-phenylethanol to other olefins such as 1-octene and 2-norbornene [13].



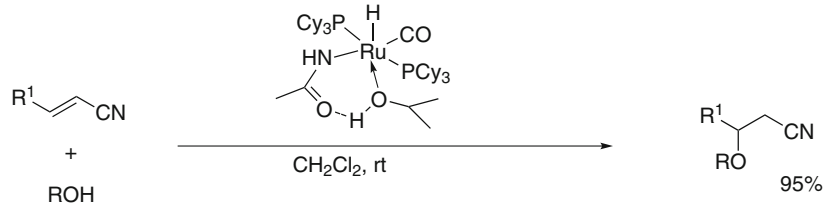
Scheme 1 Hydroalkoxylation of olefins in the presence of ruthenium catalyst precursors

The intramolecular hydroxyalkoxylation of 1,5-alk-1-enol has been reported with a catalytic system prepared from $FeCl_3$ (10 mol%) and silver triflate (30 mol%) and the reaction was carried out at 80°C in 1,2-dichloroethane (Scheme 2) [14].

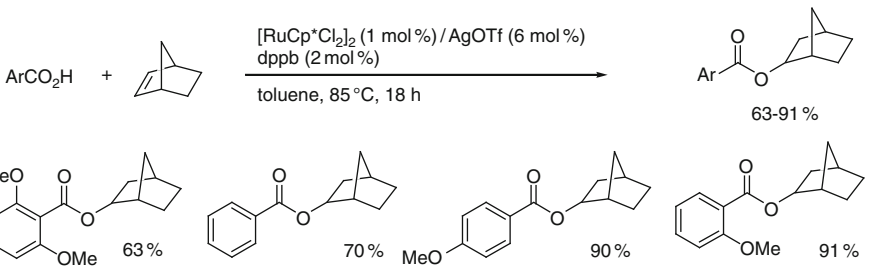
Primary and secondary alcohols have been regioselectively added to functionalized olefins such as acrylonitrile, crotonitrile, methacrylonitrile and other unsaturated nitriles in the presence of a ruthenium catalyst precursor containing an amido ligand (Scheme 3) [15, 16]. It is assumed that this Michael addition is facilitated by coordination of the nitrile group to the ruthenium centre.



Scheme 2 Intramolecular hydroxyalkoxylation catalyzed by iron catalyst



Scheme 3 Ruthenium-catalyzed hydroxyalkoxylation of acrylonitrile derivatives



Scheme 4 Ruthenium-catalyzed addition of carboxylic acids to olefins

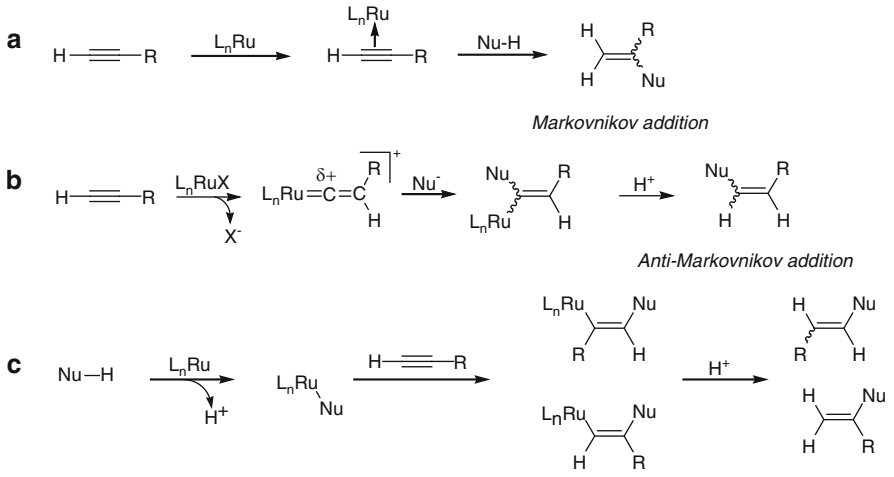
2.2 Addition of Carboxylic Acids

The catalytic system developed by Oe et al. for the addition of alcohols to olefins was slightly modified to obtain high efficiency for the addition of aromatic acids to olefins. Thus, the addition of various benzoic acids to norbornene with $[RuCl_2Cp^*]_2$/AgOTf/ diphenylphosphinobutane (dppb) as catalytic system led to high yields in the corresponding esters [17] (Scheme 4). Some limitations have appeared in this reaction as an aliphatic acid such as acetic acid was not reactive, and linear olefins required specific electronic properties. Indeed, 2-allylanisole gave the benzoate ester resulting from Markovnikov addition in 50% yield using triphenylphosphine instead of dppb, but allylbenzene was not reactive.

The addition of carboxylic acids to olefins, especially cyclic olefins has also been reported in the presence of $Fe(OTf)_3$ (2 mol%) without solvent [18]. In the same paper and others, it was shown that triflic acid that could arise from catalyst decomposition, also promoted the addition of carboxylic acids to alkenes but with lower efficacy [19, 20].

3 Addition of *O*-Nucleophiles to Alkynes

In most cases, the addition of nucleophiles to alkynes involves as the first step the electrophilic activation of the triple bond. With many Lewis acid metals, this process leads to Markovnikov addition (Scheme 5a). With metals able to facilitate



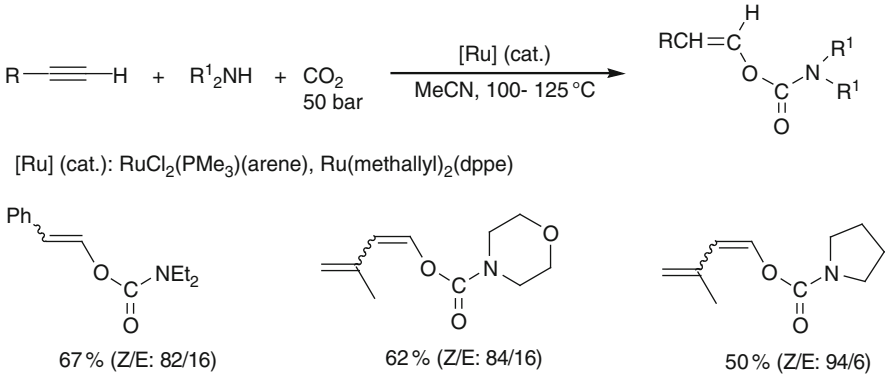
Scheme 5 Proposed mechanisms for the addition of nucleophiles to triple bonds

the isomerization of the η^2-alkyne into the η^1-vinylidene metal species, the *anti*-Markovnikov addition can take place. This is mainly the case with group 6 metals (molybdenum, tungsten, chromium), rhodium and especially with ruthenium (Scheme 5b) [21]. Other mechanisms for catalytic addition of *O*-nucleophiles to alkynes involving first activation of the nucleophile with formation of a metal–oxygen bond followed by insertion of the triple bond into the metal-*O* bond and protonolysis have also been proposed [16, 22] (Scheme 5c).

3.1 Addition of Carbamates

$Ru_3(CO)_{12}$ [23] and more efficiently mononuclear ruthenium complexes [24] catalyze the *anti*-Markovnikov addition of ammonium carbamates generated in situ from secondary amines and carbon dioxide to terminal alkynes, and selectively produce vinyl carbamates with the (*Z*)-product as major stereoisomer (Scheme 6) [24–26].

The most efficient catalyst precursors for simple alkynes were found in the $RuCl_2$(arene)(phosphine) series. These complexes are known to produce ruthenium vinylidene species upon reaction with terminal alkynes under stoichiometric conditions, and thus are able to generate potential catalysts for *anti*-Markovnikov addition [27]. In 1986, the possibility of the involvement of an active metal vinylidene in a catalytic cycle was suggested for the first time to rationalize the formation of these regioisomers [23]. Dienylcarbamates could be selectively prepared from conjugated enynes and secondary aliphatic amines but in this case, the best catalyst precursor was Ru(methallyl)$_2$(diphenylphosphinoethane) [26].



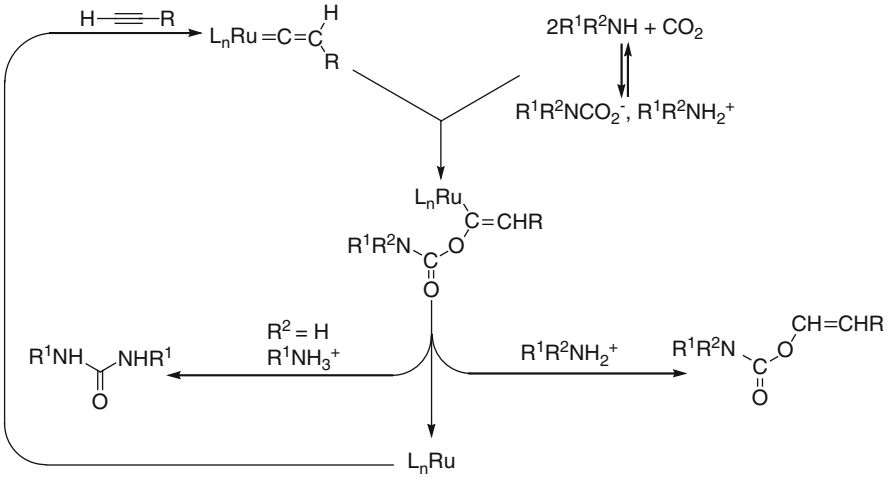
Scheme 6 Ruthenium-catalyzed synthesis of vinyl- and dienylcarbamates

The addition of carbamates to acetylene itself was also possible in the presence of ruthenium catalysts, namely $RuCl_3.3H_2O$ and the polymeric $[RuCl_2(norbornadiene)]_n$ but in relatively modest yields of 10–46% [28, 29]. The formation of vinyl carbamates is restricted to terminal alkynes, which is in line with the formation of a metal vinylidene intermediate, and also to secondary amines. However, a catalytic reaction also took place under similar conditions with primary aliphatic amines but it led to the formation of symmetrical ureas [30, 31]. The catalytic system generated in this case is thought to proceed via a ruthenium vinylidene active species and is very efficient for the formal elimination of water by formation of an organic adduct. The proposed general catalytic cycle, which applies for the formation of vinyl carbamates and ureas, is shown in Scheme 7.

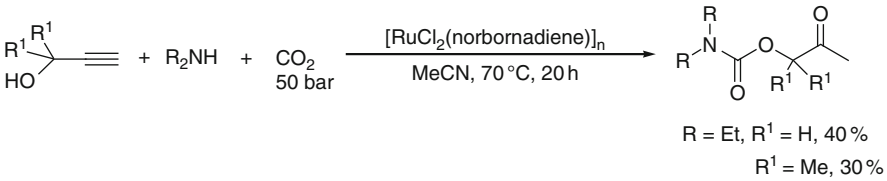
These transformations under carbon dioxide pressure have been reinvestigated recently in supercritical CO_2 without any other solvent [32]. In particular, the selection of appropriate experimental conditions and the evaluation of other ruthenium precursors such as *trans*-$RuCl_2(P(OEt_3))_4$ [33], $RuCl_2(pyridine)_4$ or $RuCl_2(benzene)(PMe_3)$ [34] have led to improvements in terms of yield and stereoselectivity.

A catalytic transformation also occurs starting from tertiary propargylic alcohols and leads to the formation of β-oxopropylcarbamates in moderate yields. These products might result from Markovnikov addition of carbamate to the terminal triple bond followed by transcarbamatation taking place in the presence of secondary amines (Scheme 8) [35]. It is noteworthy that propargylic alcohols also promote the formation of ureas from primary amines in the presence of ruthenium catalysts [30].

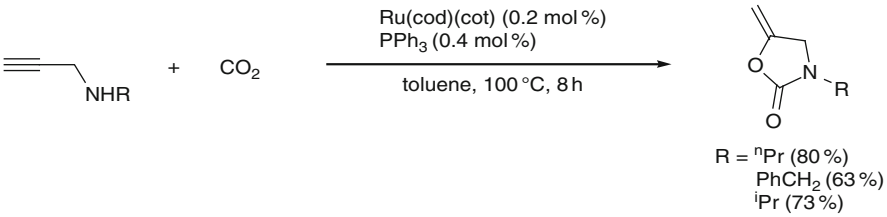
Interestingly, cyclic α-methylene carbamates were also produced via Markovnikov intramolecular nucleophilic addition of *O*-carbamates, generated in situ from a propargylic amine and CO_2, in the presence of $Ru(cod)(cot)/PPh_3$ as catalyst precursor (cod: cyclooctadiene; cot: cyclooctatriene) (Scheme 9) [36].



Scheme 7 Proposed mechanism for the formation of vinyl carbamates and ureas



Scheme 8 β-Oxopropyl carbamates from addition of carbamates to propargylic alcohols

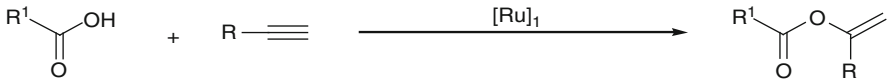


Scheme 9 Intramolecular Markovnikov addition of a carbamate to a triple bond

3.2 Addition of Carboxylic Acids

3.2.1 Markovnikov Addition

Initial studies had shown that $Ru_3(CO)_{12}$ and $[Ru(CO)_2(O_2CCH_3)]_n$ were able to promote the addition of carboxylic acids to diphenylacetylene at 145°C in toluene [37, 38]. Then, a number a catalytic systems based on ruthenium catalysts have been



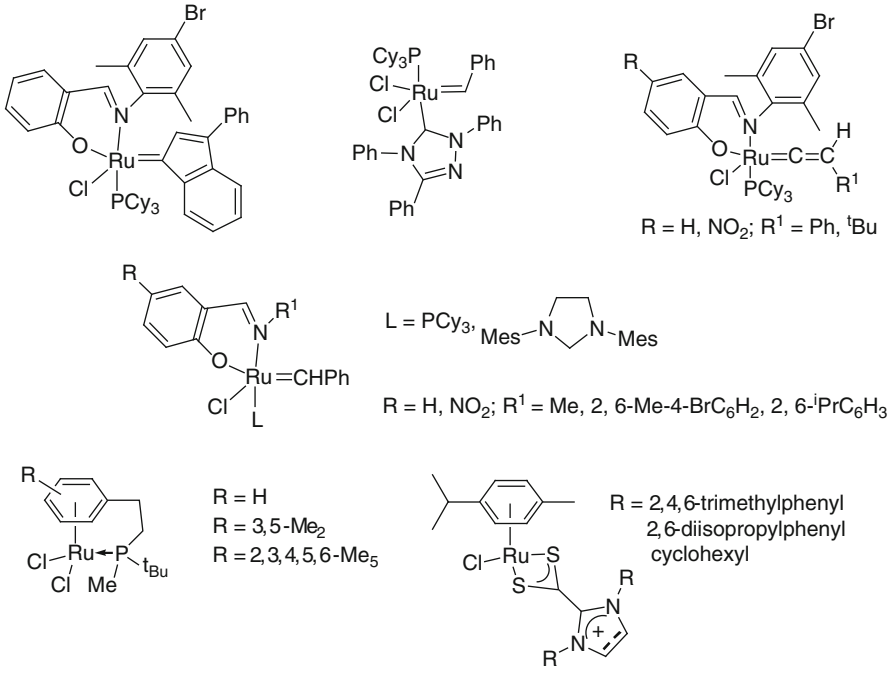
Scheme 10 Markovnikov addition of carboxylic acid to alkyne

discovered, which have made possible the Markovnikov addition of carboxylic acids to terminal alkynes to produce *geminal* enol esters according to Scheme 10.

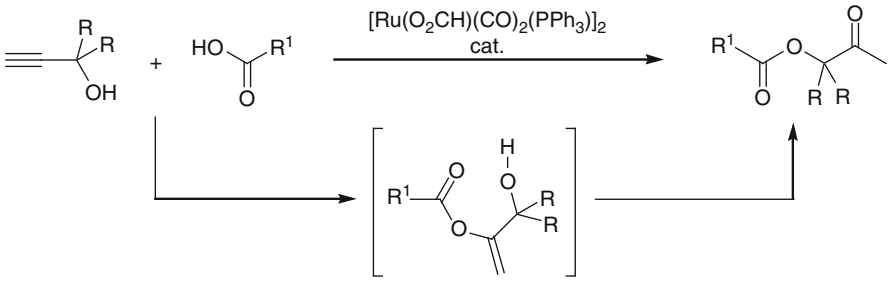
The first generation of efficient and selective catalyst precursors for the Markovnikov addition were based on $Ru^{(II)}$(bis(η^5-cyclooctadienyl) in the presence of a trialkylphosphine (PBu_3 or PCy_3) and maleic anhydride [39–43], and $RuCl_2(PPh_3)$(arene) [44–47]. A variety of enol esters have been prepared from aromatic, aliphatic alkynes, diynes and enynes [48, 49] and functionalized carboxylic acids such as aromatic and unsaturated acids [41, 46], *N*-protected amino acids [50, 51], diacids [52], α-hydroxy acids [53]. It is noteworthy that the addition takes place with retention of configuration from optically pure amino acids and hydroxy acids, and that polymers containing enol ester units have been obtained by diaddition of diacids to diynes [54]. These activated enol esters show interesting acylating properties as they liberate only a ketone as by-product under neutral conditions, and they have been used for the acylation of amines and alcohols [55, 56], the preparation of dipeptides [51], formates [57], acylamides, acylcarbamates, acylureas [58, 59], and oxalic acid derivatives [52].

Recently, new types of ruthenium catalyst precursors, which perform Markovnikov addition of carboxylic acids to terminal alkynes have been developed. The most representative examples are $[RuCl_2(p\text{-cymene})]_2$/P(furyl)$_3$/base [60], $[RuCl(PPh_3)_2(MeCN)_3]BPh_4$ [61], Ru vinylidene complexes such as $RuCl_2(PCy_3)_2(=C=CH^tBu)$, $RuCl_2(PCy_3)$(bis(mesityl)imidazolylidene)$(=C=CH^tBu)$ and the corresponding salts $[RuCl(L)_2(=C=CH^tBu)]BF_4$ [62], and ruthenium complexes with a chelating iminophenolate [63–65], a chelating phosphinoarene ligand [66], an imidazol(in)ium-2-thiocarboxylate [67] as shown in Scheme 11. The phosphinoarene complexes reported by Demonceau [66] lead to excellent regioselectivity in favour of the Markovnikov addition with turnover numbers of 5,000, which represents a very good efficacy. The catalytic behaviour of $[RuCl(PPh_3)_2(MeCN)_3]BPh_4$ can be monitored by additives. Indeed, the presence of a base such as Na_2CO_3 promotes the formation of enynes resulting from dimerization of the terminal alkyne, the classical concurrent reaction of enol formation, whereas the addition of $BF_3.Et_2O$ that helps creation of vacant site by removal of one phosphine, triggers the selective formation of *geminal* enol esters in good yields [61]. A beneficial effect of activation by microwaves is usually observed during this addition using various ruthenium precursors [66–68].

In the presence of the previous types of catalysts, propargylic alcohols did not afford hydroxy enol esters but β-ketoesters according to Scheme 12 [41, 69]. It has been shown that the first step of the reaction is actually the nucleophilic Markovnikov addition of the carboxylate to the triple bond, which is followed by an intramolecular transesterification [70, 71].



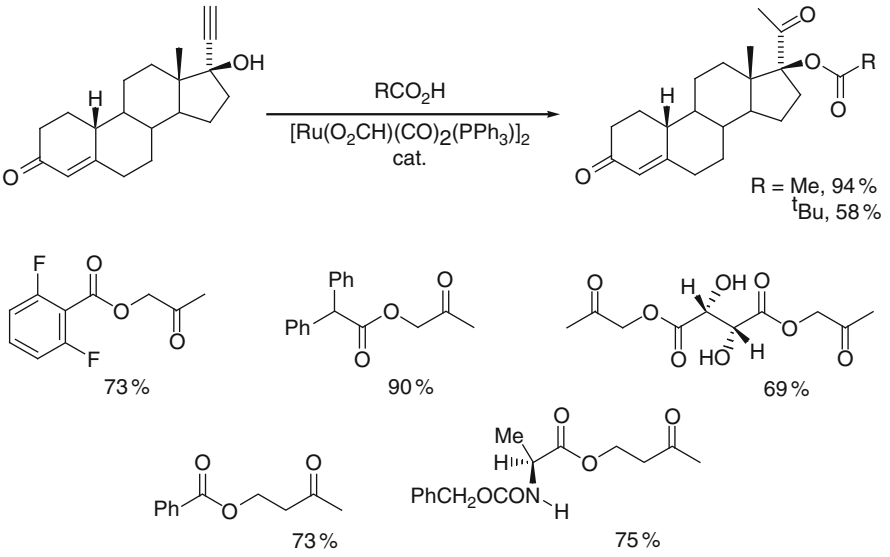
Scheme 11 Selected examples of ruthenium catalysts giving preferential Markovnikov addition



Scheme 12 Ruthenium-catalyzed addition of carboxylic acids to propargylic alcohols

The best catalyst to perform this reaction is the binuclear $[Ru(O_2CH)(CO)_2(PPh_3)]_2$ complex, which makes possible the transformation of bulky acids such as steroid derivatives [72] with retention of configuration of the starting reagents, and the preparation of β-oxopropyl esters from propargylic alcohols as well as γ-oxobutyl esters from butynol [70] (Scheme 13).

This catalyst is also very efficient to perform the addition of bulky acids to simple alkynes as shown in the synthesis of the ferrocenylcarboxylic styryl ester [73]. The mononuclear bis(carboxylate)ruthenium(II) complex *cis*-$[Ru(OAc)_2(PPh_3)_2]$ has also shown good catalytic activity for the addition of carboxylic acids to propargylic



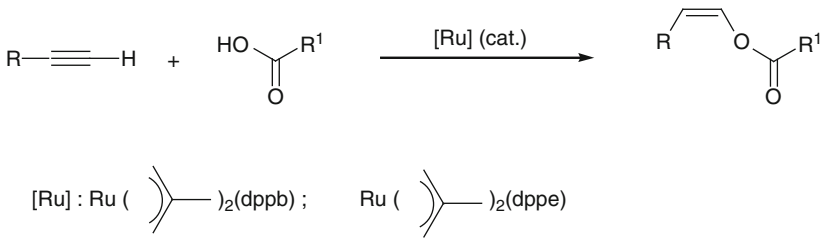
Scheme 13 Formation of β-oxopropyl and γ-oxobutyl esters

alcohols to afford β-oxopropyl esters [74]. Ruthenium complexes featuring a phosphoramidite ligand such as [$RuCl_2$((Binol)P(NR_2))(*p*-cymene) (R=Me, iPr)] are also catalytically active for the formation oxo esters from propargylic alcohols and acids at 90°C in cyclohexane as solvent [75].

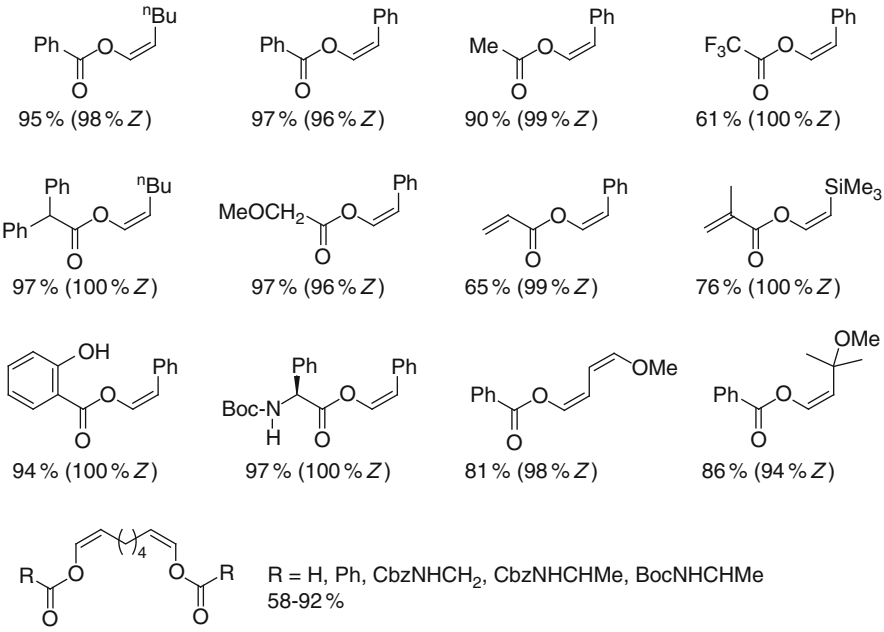
The preparation of β-oxopropyl esters has been efficiently performed in water using hydrosoluble ruthenium catalysts containing a water-soluble ligand such as PTA (1,3,5-triaza-7-phosphaadamantane), DAPTA (diacyl 1,3,5-triaza-7-phosphaadamantane) and TPPMS (sodium triphenylphosphine monosulfonate) [76, 77]. The best results illustrated by 35 examples from various carboxylic acids and propargylic alcohols at 100°C for 2–6 h in water were obtained with $RuCl_2(C_6H_6)$(TPPMS) as catalyst precursor. It is worthwhile noting that various catalysts immobilized on polystyrene [78] and inorganic supports [79, 80], as well as thermomorphic catalysts [81] have been prepared, which offer the possibility of catalyst recycling.

3.2.2 *Anti*-Markovnikov Addition

In contrast with the previous ruthenium catalysts, some π-allyl ruthenium complexes containing a chelating diphosphine ligand were the first metal complexes, which favoured the *anti*-Markovnikov addition of carboxylic acids to terminal alkynes to form (*Z*) and (*E*)-enol esters with high regio- and stereoselectivity [82–84] according to Scheme 14 . It is postulated that the catalytic cycle accounting for this regioselectivity involves a ruthenium vinylidene intermediate.



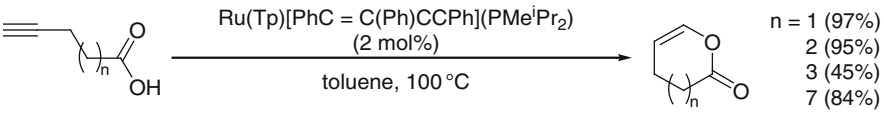
Scheme 14 *Anti*-Markovnikov addition of carboxylic acids to terminal alkynes



Scheme 15 Selected examples of *anti*-Markovnikov addition with catalysts **A** and **B**

The best catalyst precursors are Ru(methallyl)$_2$(dppb) (**A**) and Ru (methallyl)$_2$(dppe) (**B**), the choice of the appropriate complex depending on the steric demand of both the alkyne and carboxylic acid. A large variety of carboxylic acids and alkynes have been used, including *N*-protected amino acids, α-hydroxy acids and functionalized alkynes such as enynes and propargylic ethers (Scheme 15) [84, 85].

The regioselective *anti*-Markovnikov addition of benzoic acid to phenylacetylene has also been carried out with success at 111°C in the presence of ruthenium complexes containing a tris(pyrazolyl)borate (Tp) ligand, [RuCl(Tp)(cod) (**C**),

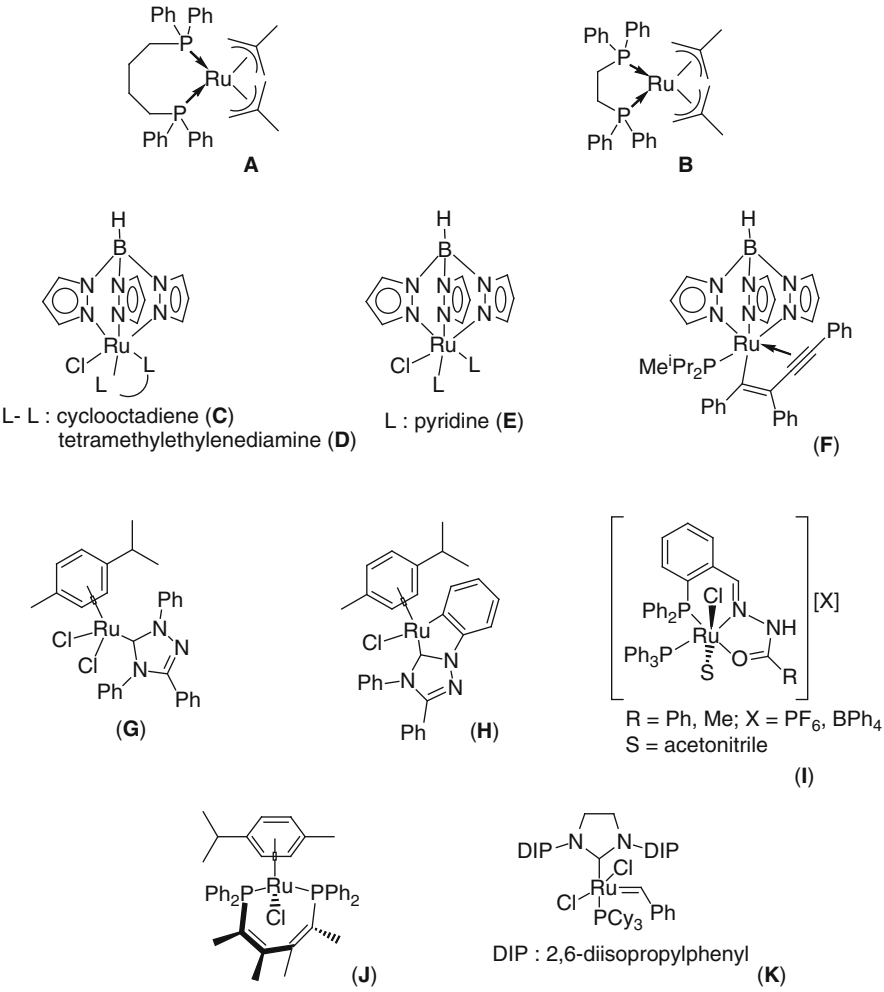


Scheme 16 *Endo*-cyclization of acetylenic carboxylic acids

RuCl(Tp)(tmeda) (**D**) RuCl(Tp)(pyridine) (**E**)], with a stereoselectivity in favour of the (*E*)-enol ester [86]. The σ-enynyl complex Ru(Tp)[PhC=C(Ph)C≡CPh)] (PMe^{i}Pr$_2$) (**F**) efficiently catalyzes the regioselective cyclization of α,ω-alkynoic acids to give endocyclic enol lactones (Scheme 16) [87].

More recently, new catalysts precursors (Scheme 17) derived from [RuCl$_2$(*p*-cymene)]$_2$ such as the RuCl$_2$(triazol-5-ylidene)(*p*-cymene) (**G**, **H**) [88] or the in situ generated catalytic system based on [RuCl$_2$(*p*-cymene)]$_2$/P(*p*-C$_6$H$_4$Cl)$_3$/DMAP [60] have revealed their potential to perform the *anti*-Markonikov addition of a variety of carboxylic acids to phenylacetylene and terminal aliphatic alkynes. RuClCp(CO)$_2$ and [RuCp(CO)$_2$]$_2$ catalyze the addition of carboxylic acids to phenylacetylene in toluene at 110°C with good efficiency and high regioselectivity towards the *anti*-Markovnikov products (in most cases >95%). It is also noteworthy that these catalysts provide the (*E*)-enol esters, which contrasts with the majority of previous catalysts, and that strong acids such as CF$_3$CO$_2$H are not reactive [89]. The same authors have developed new Ru–Re bimetallic complexes based on the RuCp(CO)$_2$ fragment. They are also active in hydrocarboxylation of terminal alkynes and regioselectively afford the *anti*-Markovnikov product even though with lower stereoselectivity than the mononuclear complex [90]. Complexes **I** [91] and **J** [92] featuring bidentate iminophosphine and diphosphine, respectively, exhibited modest reactivities for the addition of benzoic acid to terminal alkynes but excellent regioselectivity and stereoselectivity in favour of the (*Z*)-*anti*-Markovnikov products. The metathesis catalyst **K** was also able to catalyze the addition of aliphatic acids to 1-octyne and 1-heptyne at 65°C with a regioselectivity depending on the nature of the acid. Most of the acids led to Markonikov addition products as major products, but with trichloroacetic and *trans*-2-octenoic acid, the *anti*-Markovnikov products appeared to be the major enol esters [93]. With this catalyst **K**, the addition of carboxylic acids to internal alkynes was tested but at 65°C with 4 mol% catalyst loading, only trichloroacetic acid reacted to give a mixture of (*Z*) and (*E*)-isomers.

The ruthenium hydride precursor RuCl(H)(CO)(PCy$_3$)$_2$ (2 mol% loading) was found to be a highly effective catalyst for the addition of aliphatic and aromatic carboxylic acids to a variety of terminal alkynes at 90–95°C leading to complete conversion within 8–12 h. With this catalyst precursor, a strong influence of the solvent was observed. Indeed, almost perfect Markovnikov addition was obtained when the reactions were carried out in dichloromethane for both aliphatic and aromatic terminal alkynes. In contrast, in tetrahydrofuran aryl-substituted alkynes led to *anti*-Markovnikov products with high (*Z*)-selectivity, whereas aliphatic alkynes gave *geminal* enol esters, exclusively [94]. This catalyst was also very



Scheme 17 Selected examples of ruthenium catalysts giving preferential *anti*-Markovnikov addition

efficient for the addition of carboxylic acid to propargylic alcohols to form oxopropyl esters. A fine mechanistic study led the authors to propose a catalytic cycle based on the initial formation of the 16 electron species $RuCl(\eta^3\text{-}O_2CR)(CO)(PPh_3)$, which activates the alkyne. Then depending on the solvent, Markovnikov products would be formed after insertion of the alkyne into a Ru–O bond followed by protonolysis, or formation of a ruthenium vinylidene intermediate would lead to the *anti*-Markovnikov product. The influence of the solvent was also pointed out with some catalysts containing a phosphinoarene ligand as the reaction performed in water-saturated toluene were faster than those performed in dry toluene, but with the same regioselectivities [66]. It was recently shown that mononuclear ruthenium(0)

complexes were efficient catalysts for the direct formation of enol esters from terminal alkynes and carboxylic acids. A strong influence of the electronic properties of the ligands (CO, diene, phosphine) on the regioselectivity of the addition was observed, the most σ-donating ligands leading to Markovnikov addition, whereas the most π-accepting ones gave the (*E*) *anti*-Markovnikov addition, preferentially [95].

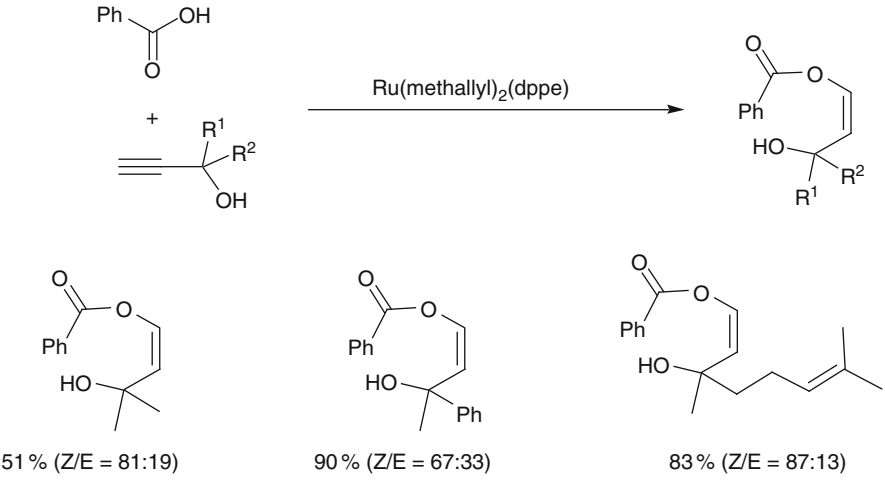
Finally, it can noted that recyclable ruthenium catalysts supported on cerium oxide prepared from $[RuCl_2(p\text{-cymene})]_2$ have been used successfully at 130°C. They favoured the formation of *anti*-Markovnikov enol esters but with moderate stereoselectivity [96].

At 65°C, the addition of carboxylic acids to propargylic alcohols in the presence of catalysts favouring the *anti*-Markovnikov addition such as $Ru(methallyl)_2(dppe)$ (**B**) led to hydroxylated alk-1-en-1-yl esters (Scheme 18) [97, 98].

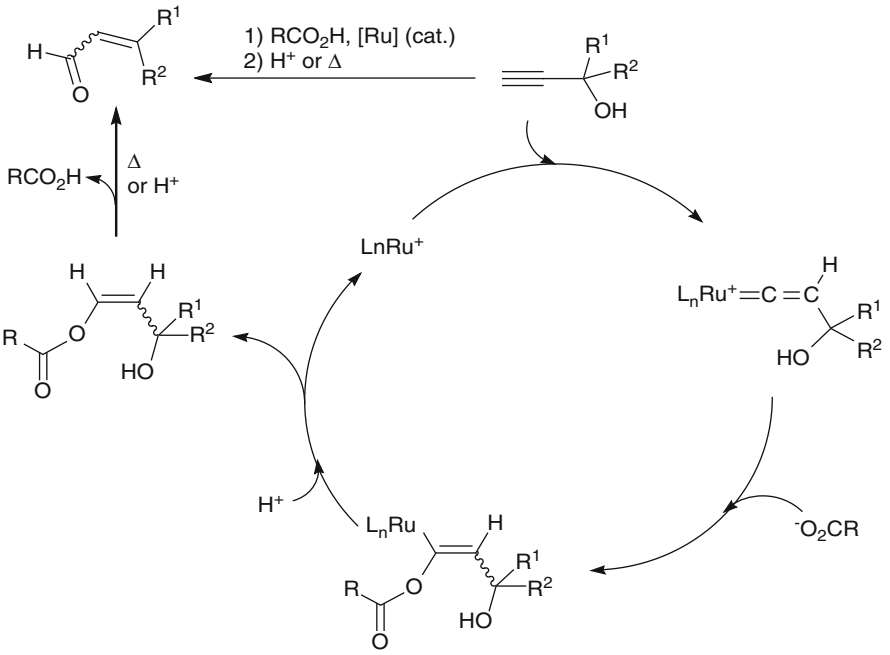
These esters can easily be cleaved under thermal or acidic conditions to give conjugated enals, corresponding to the formal isomerization products of the starting alcohols (Scheme 19).

It was recently shown that Ru(0)cyclopentadienone precursors made possible the formation of hydroxylated alk-1-en-1-yl esters in good yields with selective formation of the (*E*)-isomers from tertiary terminal propargylic alcohols (Scheme 20) [99]. On the other hand, secondary terminal propargylic alcohols led to mixtures of Markovnikov and *anti*-Markovnikov products, namely β-ketoesters and enol esters, respectively.

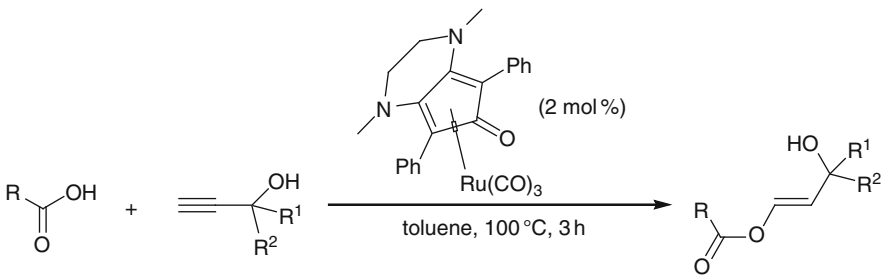
Up to now one example of ruthenium-catalyzed addition of phosphinic acid to terminal alkynes has been reported. The Markovnikov addition of diphenylphosphinic acid took place at 140°C with $Ru_3(CO)_{12}$ (2.5 mol%) as catalyst precursor and *geminal* enol esters were obtained from phenylacetylene and various aliphatic acids in high yields (Scheme 21) [100].



Scheme 18 Selective formation of β-hydroxyaldehydes



Scheme 19 *Anti*-Markovnikov addition of carboxylic acid to propargylic alcohol

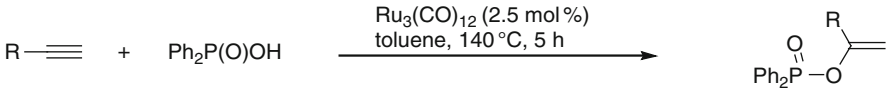


R = Me : $R^1 = R^2$ = Me (52 %) ; R^1 = Et, R^2 = Me (88 %) ; R^1-R^2 = $-(CH_2)_5-$ (85 %);
R^1 = Ph, R^2 = Me (69 %)

R = CH=CH_2 : R^1 = Et, R^2 = Me (53 %)

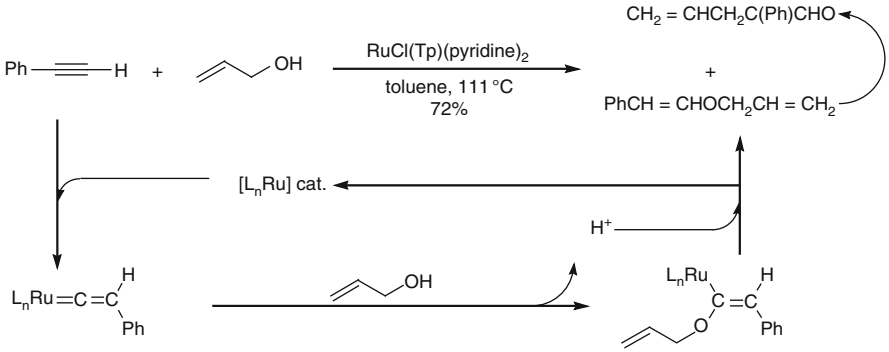
R = CH=CHPh : R^1 = Et, R^2 = Me (71 %) ; R^1–R^2 = -$(CH_2)_5$- (64 %)

Scheme 20 Selective (*E*)-*anti*-Markovnikov addition of carboxylic acid to propargylic alcohols with ruthenium(0) precursors



R = Ph (70 %), $PhCH_2$ (79 %), nC_6H_{13} (88 %), $NC(CH_2)_3$ (82 %), cyclohex-1-enyl (65 %)

Scheme 21 Addition of phosphinic acid to terminal alkynes



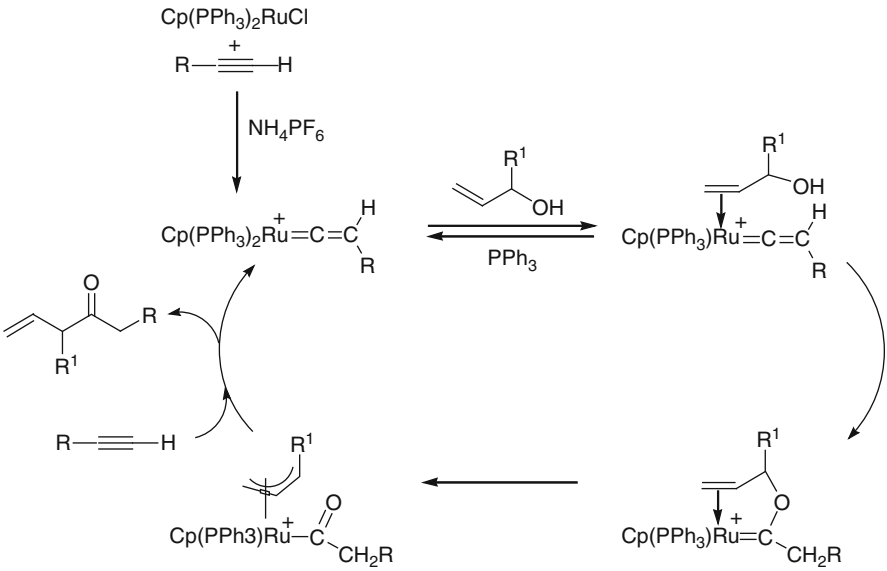
Scheme 22 Addition of allyl alcohol to phenylacetylene – Formation of vinyl ether

3.3 Addition of Alcohols

3.3.1 Addition of Allylic Alcohols

Among many methods, the addition of alcohol to alkyne is a potential method of choice to prepare vinylethers [101]. However, even though the addition of methanol to electron-deficient alkynes such as acetylene dicarboxylates is easy, the intermolecular addition of alcohol to unactivated alkynes in the presence of metal catalysts is not straightforward. With ruthenium catalysts, the only reported examples concern the addition of allylic alcohols to terminal alkynes. Thus, in the presence of a catalytic amount of RuCl(tris(pyrazolyl)borate)$(pyridine)_2$, allyl alcohol adds to phenylacetylene in refluxing toluene to produce a 1:1 mixture of allyl β-styryl ether and 2-phenylpent-4-enal (resulting from Claisen rearrangement) in 72% overall yield. (Scheme 22) [86].

A remarkable selective reaction involving first C–O bond formation followed by rearrangement and C–C bond formation occurred when Cp-containing ruthenium complexes were used as catalytic precursors. With $RuCl(Cp)(PPh_3)_2$ in the presence of NH_4PF_6, AgOTf or $In(OTf)_2$ additives, which are known to facilitate chloride abstraction from the metal centre, the addition of allylic alcohols to terminal alkynes afforded unsaturated ketones [102, 103]. The key steps of this reconstructive coupling reaction are the nucleophilic addition of the allylic alcohol



Scheme 23 Addition of allylic alcohol to alkyne followed by skeleton rearrangement

to a ruthenium vinylidene species followed by formation of an allyl-metal intermediate via sigmatropic rearrangement (Scheme 23) [103].

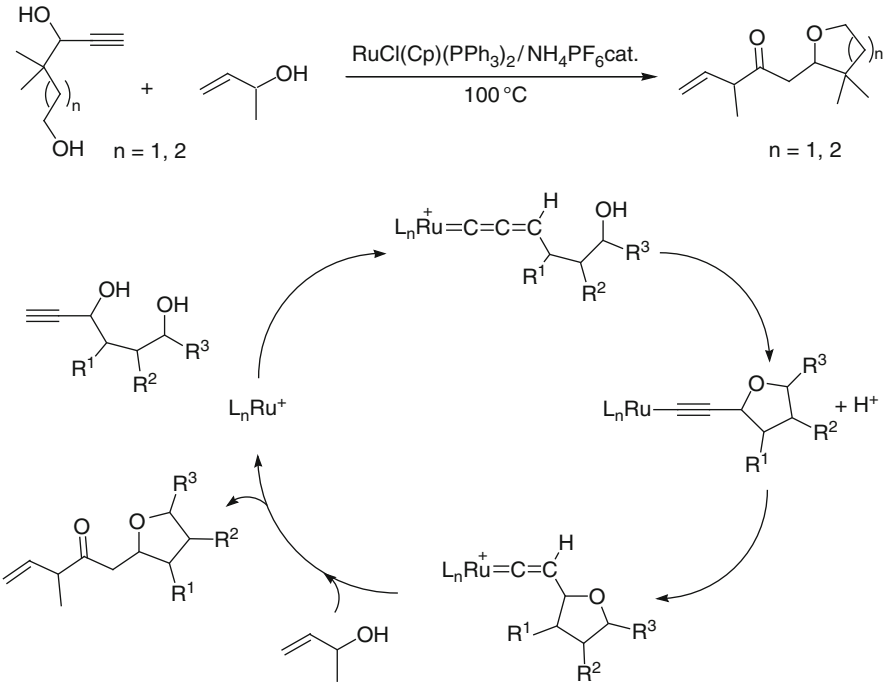
This transformation of terminal alkynes via coupling with allylic alcohol and formation of a C–C bond with atom economy has been applied to the synthesis and modification of natural compounds such as rosefuran and steroids [104, 105].

As an extension of this reaction, the selective intramolecular nucleophilic addition of an hydroxy group at Cγ of a ruthenium allenylidene species generated by activation of propargylic alcohol by $RuCl(Cp)(PPh_3)_2/NH_4PF_6$ provides a ruthenium vinylidene intermediate, which reacts with allylic alcohol via a second nucleophilic addition as described above (Scheme 24) [106]. This unprecedented tandem reaction makes possible the construction of tetrahydrofuran derivatives in good yields and has been used in the multistep synthesis of (−)calyculin A [107].

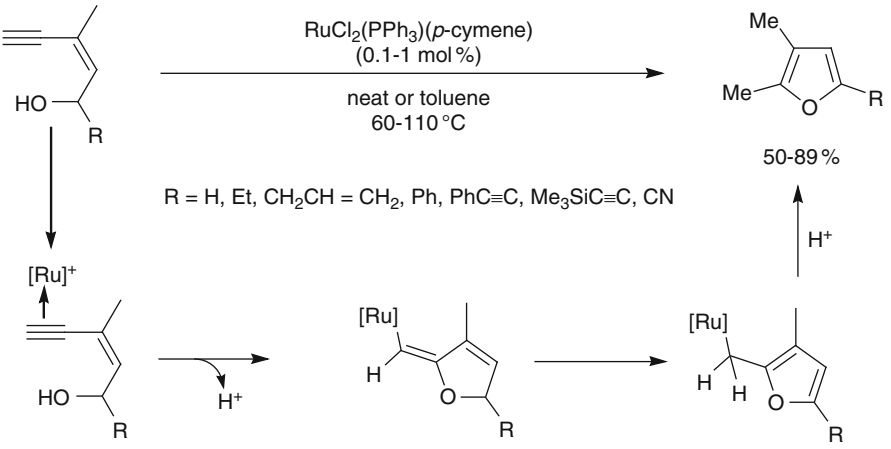
3.3.2 Intramolecular Addition of Hydroxy Group to Triple Bond

The intramolecular addition of an hydroxy group to a triple bond has been performed successfully in the presence of $RuCl_2(PPh_3)$(*p*-cymene) as catalyst precursor under mild conditions [108, 109]. The Lewis acid properties of the ruthenium active species provide the activation of the triple bond and the Markovnikov addition of the hydroxy group to form 2-methylfuran derivatives after 1,5-proton shift and aromatization (Scheme 25).

All the ruthenium-catalyzed cycloisomerizations of acetylenic alcohols that will be described from now on involve only terminal triple bonds. They correspond to



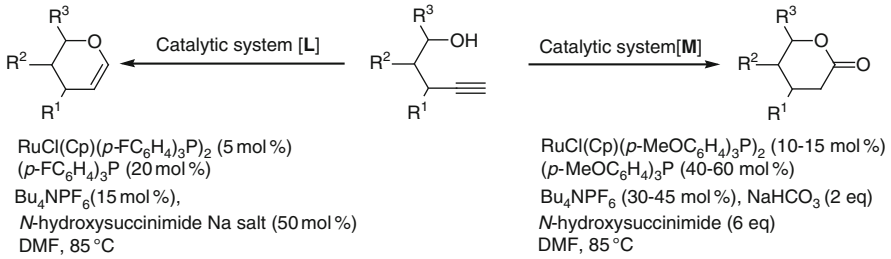
Scheme 24 Double addition to propargylic alcohol derivatives



Scheme 25 Formation of furans from Z-enynols

endo cyclization processes that have been rationalized by the intermediate formation of ruthenium vinylidene as active catalytic species.

Starting from pent-4-yn-1-ols (bis-homopropargylic alcohols), the catalytic system [**L**] based on RuCl(Cp)(tris(*p*-fluorophenyl)phosphine)$_2$ (5 mol%), tris



Scheme 26 *Endo*-cyclization of bis-homopropargylic alcohols with catalytic systems **L** and **M**

(*p*-fluorophenyl)phosphine (20 mol%), Bu_4NPF_6 (15 mol%) and *N*-hydroxysuccinimide sodium salt (50 mol%) led to the selective formation of cyclic enol ethers via intramolecular *anti*-Markovnikov addition of the hydroxy group to the terminal carbon of the triple bond [110].

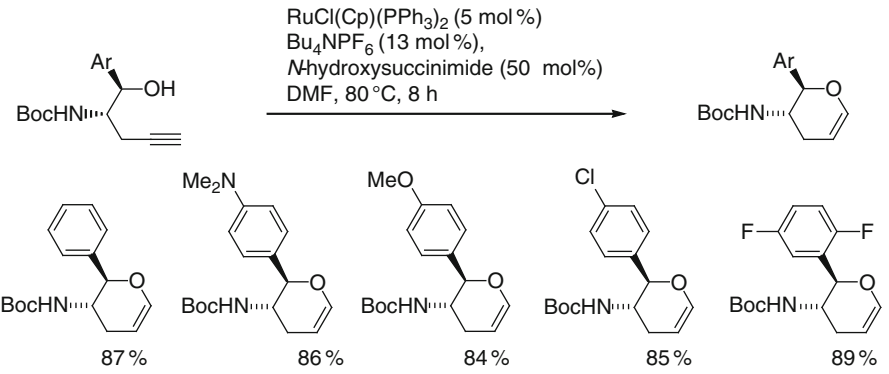
However, in the presence of (cyclopentadienyl)ruthenium complexes bearing an electron-rich ligand such as tris(*p*-methoxyphenyl)phosphine in the presence of a large excess of the same ligand (catalytic system **M**), the selective formation of lactones was obtained. The elimination of the organic ligand as a six-membered lactone was made possible by oxidation of an intermediate cyclic alkoxycarbene-metal with *N*-hydroxysuccinimide, a mild oxidant which did not destroy the catalyst (Scheme 26) [110].

Both oxidative cyclization and cycloisomerization were applied to a variety of substrates including sugar derivatives, the only restriction to the formation of lactones was the presence of a tertiary alcohol functionality. The presence of a heteroatom at the propargylic position also inhibited both catalytic reactions.

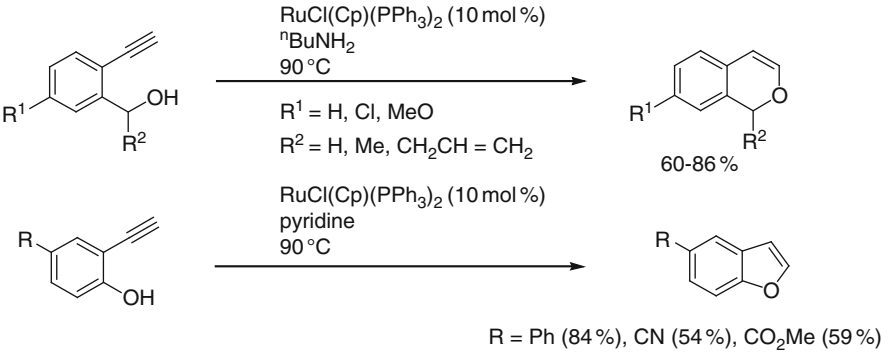
4-Amino-bis-homopropargylic alcohols have been recently cyclized to form dihydropyrans with a catalytic system inspired from (**L**) in Scheme 26 [111]. $RuClCp(PPh_3)_2$ (5 mol%) was used as catalyst precursor in association with Bu_4NPF_6, N-hydroxysuccinimide and $NaHCO_3$ in DMF at 80°C and led to excellent yields. The amino functionality that would lead to a five-membered pyrroline upon cyclization was not reactive in the presence of the hydroxy group, whereas it was when the OH group was protected. This fact reveals the high chemoselectivity of this endocyclization (Scheme 27).

An organic base such as butylamine or pyridine has been associated as the only additive to the same ruthenium precursor to generate another active catalyst. It was used to perform the *endo*-cyclization of 2-ethynylbenzylalcohols and 2-ethynylphenols into the corresponding isochromenes and benzofurans (Scheme 28) [112]. It is noteworthy that from an acetylenic substrate containing both benzyl alcohol and phenol functionalities, a high chemoselectivity in favour of the formation of furan via 5-*endo*-cyclization was observed.

Surprisingly, from homopropargylic substrates incorporating a cyclopentanol unit, the Markovnikov addition affording a bicyclic [3,3,0] structure, was observed when $RuCl_2(PCy_3)_2(=CHPh)$ was used as catalyst in toluene at 80°C [113].

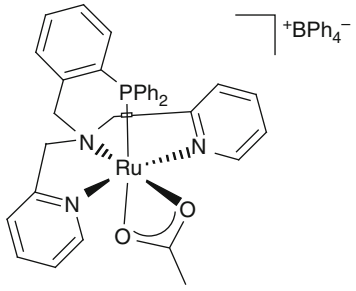


Scheme 27 *Endo*-cyclization of bis-homopropargylic alcohols with $RuClCp(PPh_3)_2$ as precursor

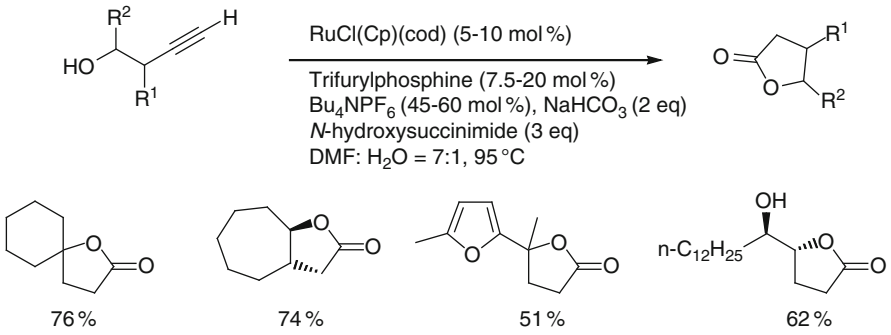


Scheme 28 *Endo*-cyclization of acetylenic benzylic alcohols and phenols

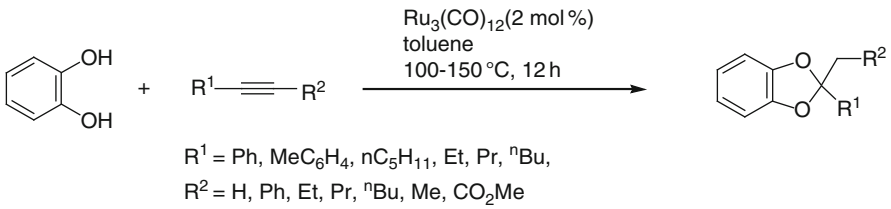
Scheme 29 Efficient ruthenium catalyst for acetylenic alcohols cyclization



Recently, the cyclization of pent-4-yn-1-ols and but-3-yn-1-ols via *anti*-Markovnikov addition of the hydroxy group to the terminal carbon of the triple bond with a ruthenium catalyst in THF at 80°C and no other additive has been reported. All types of acetylenic alcohols, purely aliphatic and including a phenylacetylene fragment have been cycloisomerized in excellent yields. The catalyst is a cationic ruthenium(II) complex has depicted in Scheme 29 [114].



Scheme 30 Formation of pentalactones from homopropargylic alcohols



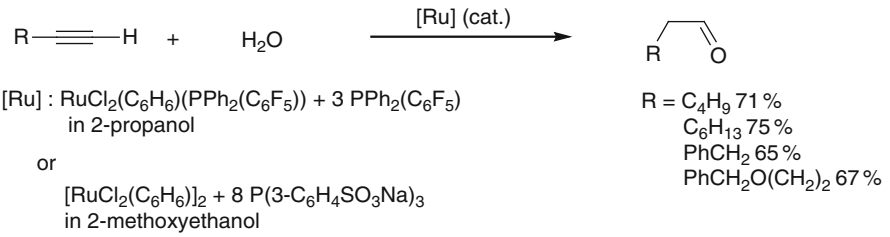
Scheme 31 Double OH addition of catechol to alkynes

Homopropargylic alcohols (but-3-ynols) as well as propargylic epoxides and pentynols readily form cyclic ruthenium alcoxycarbenes upon intramolecular nucleophilic addition of the OH group to the electrophilic α-carbon of ruthenium vinylidene species. Their oxidation in the presence of *N*-hydroxysuccinimide leads to the formation of pentalactones. The best catalytic system reported up to now for this transformation of but-3-ynols is based on $RuCl(C_5H_5)(cod)$, tris(2-furyl)phosphine, $NaHCO_3$ as a base, in the presence of nBu_4NBr or nBu_4PF_6, and *N*-hydroxysuccinimide as the oxidant in DMF-water at 95°C (Scheme 30) [115].

The double addition of catechol to alkynes appears as an unpredicted intermolecular reaction. Indeed, in the presence of 2 mol% $Ru_3(CO)_{12}$ in toluene at 100–150°C in a sealed tube the double addition of the 2 phenolic *ortho*-OH took place at the same acetylenic carbon of the triple bond to form 1,3-benzodioxoles in good yields from terminal and internal alkynes as well (Scheme 31) [116]. When the alkyne is terminal, the final product results from Markonikov addition.

3.4 Addition of Water

The catalytic hydration of alkynes with a variety of ruthenium catalysts has been recently reviewed [117]. The addition of water to terminal alkynes catalyzed by



Scheme 32 *Anti*-Markovnikov hydration of terminal alkynes

ruthenium(III) complexes leads to ketones following Markovnikov's rule [118–120]. The use of $RuCl_2(C_6H_6)(PPh_2(C_6F_5))$ in the presence of 3 equivalents of $PPh_2(C_6F_5)$ (**N**) , or $[RuCl_2(C_6H_6)]_2$ associated to 8 equivalents of the water-soluble ligand $P(3\text{-}C_6H_5SO_3Na)_3$ (TPPTS) (**O**) in alcohol at 65–100°C provides the selective formation of aldehydes resulting from *anti*-Markovnikov addition (Scheme 32) [121].

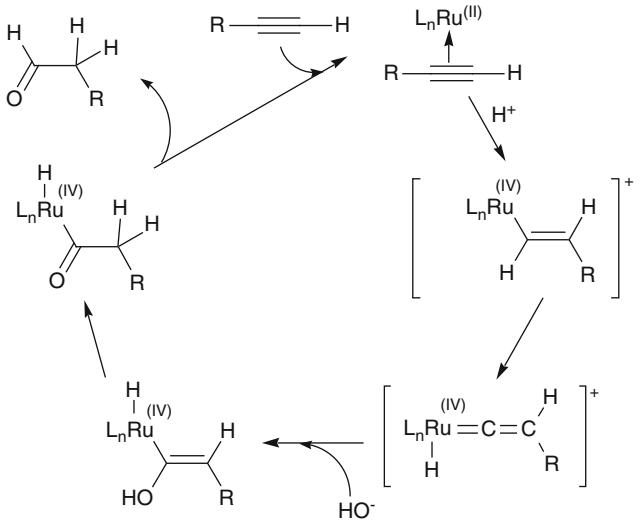
A variety of linear aliphatic terminal alkynes were transformed into aldehydes with good selectivity. The efficiency, regioselectivity of the addition, substituent tolerance were improved by using RuCl(Cp)(phosphine)$_2$ (**P**) (Scheme 34) or RuCl (Cp)(diphosphine) as catalyst precursor [122]. The best results were obtained with diphenylphosphinomethane (dppm) as ligand, which made possible the preparation of aldehydes from bulky aliphatic alkynes (*tert*-$BuCH_2CHO$ (81%)), aromatic alkynes ($PhCH_2CHO$ (90%)), diynes ($OHCCH_2(CH_2)_6CH_2CHO$ (89%)) and functional terminal alkynes ($NC(CH_2)_3CH_2CHO$ (88%), $PhCH_2O(CH_2)_2CH_2CHO$ (94%)).

The mechanism of this reaction was investigated in details by isolation of intermediates, deuterium-labelling experiments and DFT calculations [123]. The postulated catalytic cycle involves first protonation of a ruthenium(II)-alkyne species to give a Ru(IV)-vinylidene intermediate via a Ru(IV)-vinyl species. The nucleophilic addition of water to the α-carbon of the vinylidene ligand followed by reductive elimination affords the aldehyde (Scheme 33).

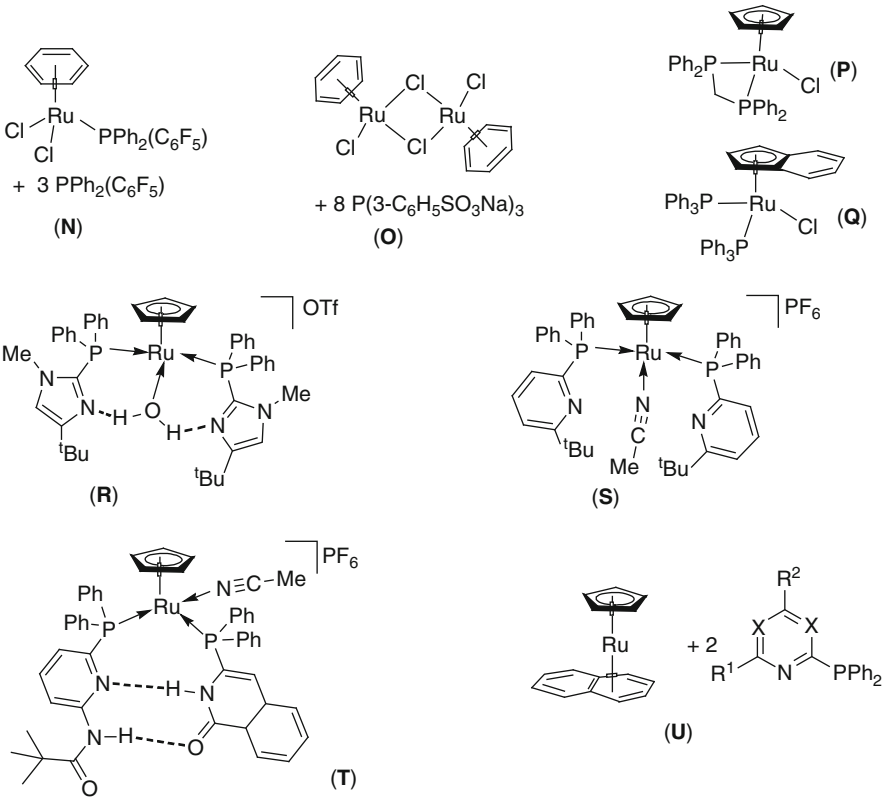
The indenyl complex $RuCl(\eta^5\text{-}C_9H_7)(PPh_3)_2$ (**Q**) (Scheme 34) also provides an efficient catalyst precursor for the *anti*-Markovnikov hydration of terminal alkynes in aqueous media and micellar solutions in the presence of surfactants such as sodium dodecylsulfate (SDS) or hexadecyltrimethylammonium bromide (CTAB) [124] (Scheme 35). Notably, this system can be applied to the hydration of propargylic alcohols to selectively produce β-hydroxyaldehydes.

In contrast, the reaction of secondary propargylic alcohols in 2-propanol/H_2O at 100°C in the presence of 5 mol% of RuCl(Cp)$(PMe_3)_2$ leads to conjugated enals with (*E*)-stereoselectivity (formal Meyer Schuster rearrangement products) (Scheme 36) [125].

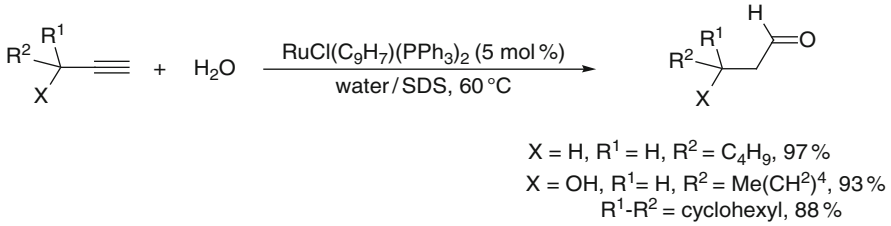
The formation of β-hydroxyaldehydes from propargylic alcohols has also been observed in aqueous media in the presence of a catalytic amount of water-soluble ruthenium sulfophthalocyanine complex and the heterogeneous ruthenium hydroxyapatite catalyst [126].



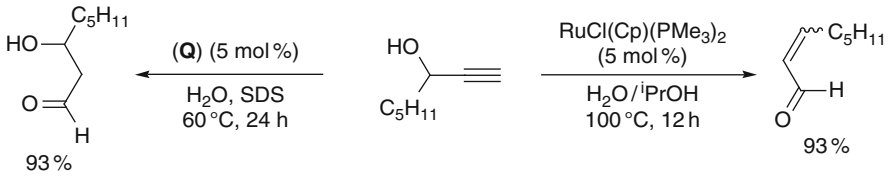
Scheme 33 Proposed mechanism for ruthenium catalyzed hydration of terminal alkynes



Scheme 34 Some catalysts for *anti*-Markovnikov addition of water



Scheme 35 Hydration of alkynes in aqueous medium

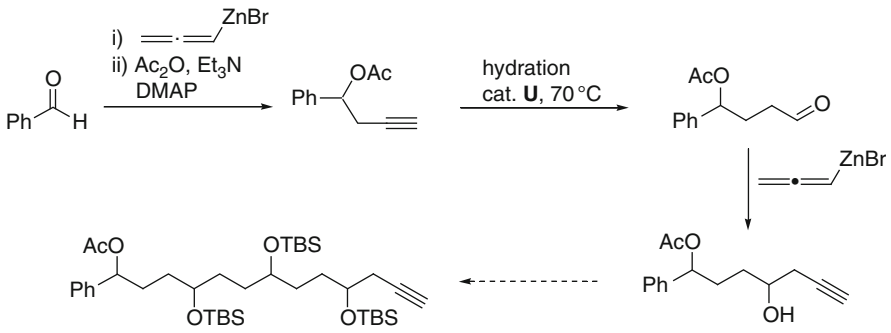


Scheme 36 Two hydration processes involving ruthenium vinylidene intermediates

Recently, a new class of supramolecular CpRu-containing catalysts for *anti*-Markovnikov hydration of alkynes has emerged [127–135]. The remarkable activity of catalytic systems such as **R–T** (Scheme 34) in terms of reactivity and selectivity is based on the principle of cooperative catalysis between the metal centre, the functional groups of the ligands, and the substrates driven by hydrogen bonding. Recent investigations by Grotjahn have shown that a bifunctional mechanism is involved in which the formation of the vinylidene and the addition of water are accelerated by hydrogen bonding interactions [129, 132–134]. In complexes such as **T**, the self-assembled monophosphine ligands behave as a diphosphine with large bite angle [135] and confer a high reactivity to the ruthenium centre. Based on the same concept, active catalysts have been formed upon treatment of the air-stable ruthenium(naphthalene)(cyclopentadienyl) hexafluorophosphate with 2 equivalents of pyridine–phosphine or triazine–phosphine ligand (**U**). With this system, very high efficiencies and selectivities were obtained for a wide range of functional terminal alkynes at moderate temperature (45–65°C) [131]. The *anti*-Markovnikov hydration of terminal alkynes with catalysts prone to supramolecular interactions has been used in sequential hydration–alkynylation reactions for the synthesis of polyols (Scheme 37) [136, 137].

The ruthenium catalysts obtained by grafting [$RuCl_2$(*p*-cymene)] units onto dendrimers have been used in aqueous media to perform hydration of terminal alkynes. A slightly positive dendritic effect was observed on selectivity towards ketone formation when the reaction was performed in water [138].

The stoichiometric hydration of terminal alkynes to form ketones was carried out with $FeCl_3$ in dichloromethane at room temperature [139]. Only recently, the utilization of $FeCl_3$ (10 mol%) in 1,2-dichloroethane under air gave access to a



Scheme 37 Iterative sequences involving *anti*-Markovnikov hydration

catalytic procedure [140]. A variety of acetophenone derivatives with various substituents in *para*-position on the phenyl group were thus prepared in excellent yields.

4 Conclusion

Among group 8 metals, ruthenium catalysts appear to be the most efficient organometallic species able to perform addition of *O*-nucleophiles to olefins and alkynes. Starting from olefins, the addition of alcohols and carboxylic acids is essentially of Markovnikov type, and requires the presence of additives, especially silver triflate, to generate active species. Starting from alkynes, Markovnikov and *anti*-Markovnikov additions can take place, depending on the nature of the ruthenium precatalyst. Markovnikov addition of carboxylic acid and water are driven by the Lewis acidity of the ruthenium centre and lead to *geminal* enol esters and ketones, respectively. The umpolung of terminal triple bonds via ruthenium vinylidene formation is a unique tool to trigger the addition of nucleophiles at the terminal carbon atom of the triple bond. This mechanism has been evoked for most of the *anti*-Markovnikov additions to terminal alkynes. Thus (*Z*)- and (*E*)-enol esters from carboxylic acids, aldehydes from water, (*Z*)- and (*E*)-vinyl carbamates from ammonium carbamates and cyclic vinyl ethers were prepared with selected ruthenium catalysts. It is noteworthy that intermolecular addition of alcohols to alkynes has not been successful with group 8 metals, whereas several ruthenium catalysts efficiently perform intramolecular addition leading to cyclic unsaturated ethers via *endo*-cyclization. Group 8 metal catalysts complement the metals of the other groups, and ruthenium offers an additional possibility of fine tuning the Markovnikov and *anti*-Markovikov additions of *O*-nucleophiles to triple bonds thanks to easy modification of the properties of catalyst precursors via coordination of suitable ligands.

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Groups 9 and 10 Metals-Catalyzed O–H Bond Addition to Unsaturated Molecules

Giorgio Abbiati, Egle M. Beccalli, and Elisabetta Rossi

Abstract Progress in the field of inter- and intramolecular additions of oxygen nucleophiles (water, alcohols, phenols, and carboxylic acids) to alkenes, allenes, alkynes, and nitriles catalyzed by Co, Rh, Ir, Ni, Pd, and Pt is critically reviewed.

Keywords Catalysis · Hydration · Hydroacyloxylation · Hydroalkoxylation · Multiple bonds · Oxygen nucleophiles

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1 Introduction

Transition-metal complexes continue to play a relevant role in organic synthesis. They can realize selective transformations that would be either difficult or impossible to attain by conventional organic chemistry. The addition of heteroatom-hydrogen (Het–H) bonds across the carbon–carbon bond of unsaturated molecules, under transition-metal catalysis is a very important process from the synthetic point of view because these addition reactions can be performed with 100% atom efficiency, and for this reason they fulfill the requirements of atom economy. Contrary to the broad application of nitrogen nucleophiles in metal-transition catalyzed reactions, the use of oxygen nucleophiles has remained a less explored area due to the diminished nucleophilicity of this atom compared to nitrogen. The formation of carbon–oxygen (C–O) bonds continues to stimulate considerable interest considering the wide presence of oxygen-containing heterocyclic structures in natural products and medicinally important compounds.

The literature reports several general reviews on this topic [1–8] regarding all the transition metals. In this chapter, we consider the use of catalysts of 9–10 group metals, Co, Rh, Ni, Ir, Pd, and Pt with the aim to provide an update of methodological progresses. When appropriate, references to older works have been added. Different types of C–O functionalities may be formed by addition of oxygen nucleophiles to unsaturated bonds. The reaction typologies considered are: hydrations, hydroalkoxylations, and hydroacyloxylations of alkenes, allenes, alkynes, and nitriles, reported as both intramolecular and intermolecular processes.

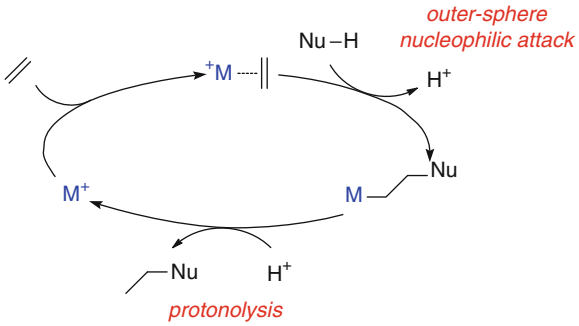
The nature of the transition-metal complex plays a key role in all these reactions and the main problem is to find the proper catalyst, which should be not only efficient but also relatively cheap and stable.

Hydration reactions are of great interest to the chemical industry when performed on functionalized alkynes because the resultant ketones are useful as chemical intermediates. Thus, in order to develop nonmercury alkyne hydration catalysts, the metals of the nine and ten groups were studied, in particular Ir, Rh, Pd, and Pt. Nucleophilic attack on a C–C multiple bond by the OH group of alcohols or phenols results in an hydroalkoxylation reaction. In this field, the palladium catalysts dominate by far. For example, the comparison between Pd and Pt catalysts in the activation of alkynes toward the intermolecular addition of alcohols showed a much slower reaction with the homologous Pt complex, probably due to the higher stability of the Pt–C bond in the vinylplatinum complex. The use of carboxylic acids as nucleophiles on the C–C multiple bonds results in hydroacyloxylation reaction (hydroacetoxylation when acetic acid is used). This reaction is one of the most important processes for the synthesis of unsaturated and saturated carboxylic esters as well as for the achievement of saturated and unsaturated lactones starting from a wide range of acyclic alkenoic and alkynoic acids.

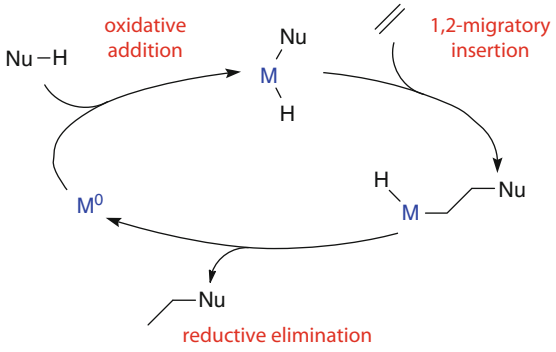
In comparison with other addition reactions, the C–O bond formations proceed under milder conditions, giving higher yields of the products, proceeding with good or excellent regio- and stereoselectivities. The reaction mechanisms can be quite

different depending on the unsaturated substrate and the transition metal involved. Considering the alkenes, two potential mechanisms are most commonly accepted. The key step is the reaction of a metal–olefin complex with a nucleophile to give a β-substituted metal–alkyl species. This transformation can in principle proceed through an inner-sphere or an outer-sphere mechanism, with opposite stereochemical outcomes, and with different implications for catalyst design. Mechanistic studies, both experimental and theoretical, have demonstrated that either pathway in fact can be operative. Scheme 1 depicts the coordination of a C–C double bond to an electrophilic metal center activating the unsaturated system toward outer-sphere attack by a protic nucleophile NuH. The newly formed M–C bond is then cleaved by protonolysis to regenerate the catalyst.

Scheme 2 shows an alternative inner-sphere mechanism, first involving the initial oxidative addition of NuH to the metal followed by olefin insertion into the M–Nu bond. The resulting M–C bond is cleaved by a C–H reductive elimination or by protonolysis (Scheme 2).While this mechanism is generally preferred for more electron-rich metals such as rhodium and iridium, several studies suggest that platinum and palladium-catalyzed additions of N–H or O–H nucleophiles more likely run by the outer-sphere electrophilic activation mechanism shown in Scheme 1.



Scheme 1 Outer-sphere mechanism



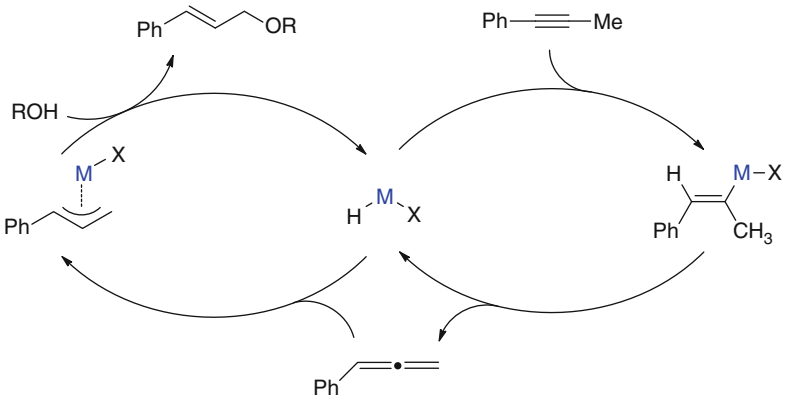
Scheme 2 Inner-sphere mechanism

Both palladium(II) and platinum(II) catalysts are quite efficient in the promotion of nucleophilic addition to a coordinated olefin, but their distinct properties often lead to complementary M–C bond cleavage, pathway required to obtain product. Specifically, as palladium complexes are reactive toward ligand substitution, thus facilitating the β-hydride elimination, in contrast, platinum complexes are relatively inert toward ligand substitution. This facilitates the development of alternative pathways for M–C bond cleavage, such as protonolysis, and reduces the problems caused by competing olefin-isomerization reactions.

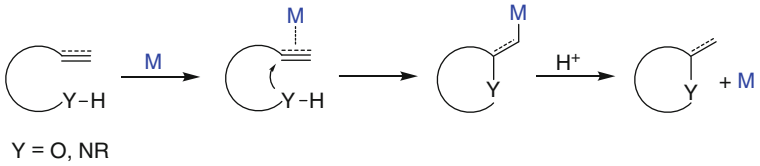
Starting from alkynes, the formation of allene intermediate was proposed followed by the intermediacy of the π-allyl-metal complex, which undergoes the attack of the oxygen nucleophile to give allyl ethers (Scheme 3).

The utilization of carbon–carbon unsaturated compounds containing proximate oxygen nucleophiles, exploiting the carbon–oxygen bond formation, represents one of the most versatile and efficient methods for the preparation of oxygen-containing heterocycles such as furan, pyran, benzofuran, and benzopyran derivatives among others. In this case, the intramolecular attack of the heteroatom to the electron-deficient unsaturated system produces a new heterocyclic organometallic intermediates, converted to product by protonolysis (Scheme 4).

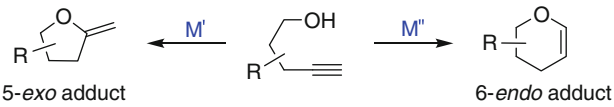
A particular mention regards the impact of the transition-metal catalysis on the regioselectivity. In the presence of Ir, Pd, Pt, and Rh, a particular regioselectivity was reported, 5-*exo*-dig vs 6-*endo*-dig, depending on the substrate, the transition-metal and the reaction conditions (Scheme 5).



Scheme 3 Intermolecular mechanism of addition to alkynes



Scheme 4 Intramolecular mechanism of addition to alkynes



Scheme 5 Regioselectivity on intramolecular reaction of alkynols

Finally, the coordination and reactivity of nitriles with low-valent late transition-metal complexes is of interest because catalytic hydration of nitriles to amides remains a challenging goal. The development of catalytic reactions that employ transition-metal complexes as catalysts under neutral and mild conditions has been proposed as a particularly important alternative for the nitrile hydration process and considerable efforts have been spent in this direction.

2 Cobalt

Several cobalt compounds are widely used as oxidation catalysts. Cobalt-based catalysts are also important in some industrial process such as the Fischer–Tropsch process [9] and the hydroformylation of alkenes [10]. Also, the cross-coupling reactions promoted by this metal have been recently highlighted [11]. Conversely, cobalt is not a suitable metal catalyst for the O–H addition to alkynes, alkenes, and nitriles.

2.1 Hydration

Catalytic activity on alkynes has not been reported, whereas some isolated and peculiar examples of hydration of alkenes and nitriles have been reported promoted by aminocomplexes of this metal.

2.1.1 Alkenes

Sargeson and coworkers studied the hydration of coordinated carboxyalkenes using bis(alkanediamine)cobalt(III) complexes with either methyl maleate or ethyl fumarate *cis* coordinated to a water molecule [12] (Fig. 1).

The authors established, by ^{18}O-tracer experiments and three-dimensional X-ray crystallographic analysis, that the reaction involved an intramolecular cyclization reaction with the exclusive formation of a five-member ring in the chelated products and suggested that $[(1,3\text{-propanediamine})_2Co(OH)(OH_2)]^{2+}$ ion could be an effective reagent to hydrate alkenes of this type.

2.1.2 Nitriles

Seminal works involved the base promoted hydration of acetonitrile to acetamide in the presence of substitutionally inert $[Co(NH_3)_5]^{3+}$ as coordinating agent. Related

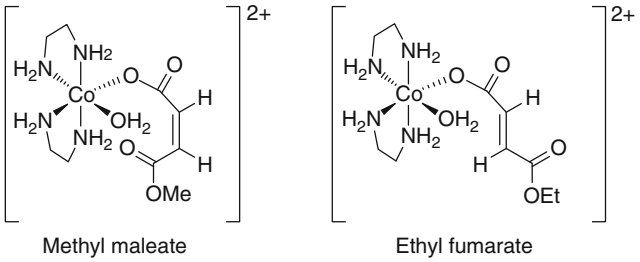


Fig. 1 Bis(alkanediamine)cobalt(III) complexes with maleate and fumarate

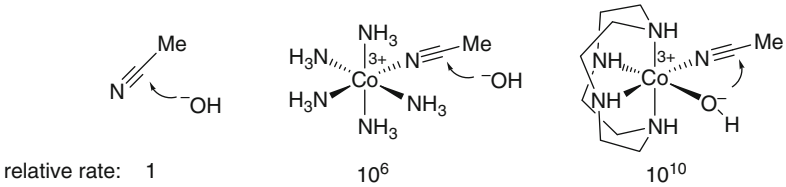


Fig. 2 Rate acceleration in nitrile hydration promoted by $[Co(cyclen)(OH_2)_2]^{3+}$

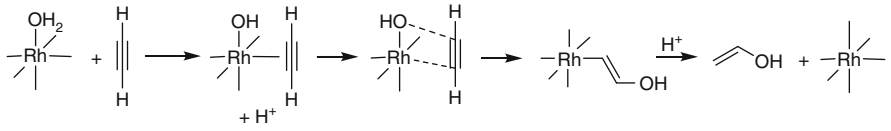
studies suggested that the hydrolysis occurs by attack of free hydroxide anion on the nitrile carbon atom. The hydrolysis of coordinated acetonitrile showed a 10^6-fold rate acceleration with respect to simple alkaline hydrolysis [13, 14] (Fig. 2). However, Co(III) complexes tend to be poor catalysts giving little or no catalytic turnover because of slow ligand exchange rates, but they often provide valuable mechanistic information by forming stable intermediates. An example of a real effective Co(III) catalyzed hydration of nitriles has been reported by Chin and coworkers [15, 16]; $[Co(cyclen)(OH_2)_2]^{3+}$ efficiently catalyzes hydration of acetonitrile to acetamide in a three-step cycle (cyclen = 1,4,7,11-tetraazacyclododecane). The mechanism involves coordination of the nitrile to the cobalt complex followed by intramolecular metal hydroxide attack on the nitrile and dissociation of the chelated amide. Interestingly, the simultaneous Lewis acid activation and metal hydroxide activation provides over a 10^{10}-fold rate acceleration for the hydration reaction (Fig. 2).

3 Rhodium

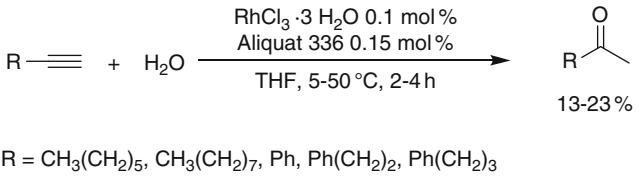
3.1 Hydration

3.1.1 Alkynes

The first study on Rh catalyzed hydration of acetylene was published in 1969 by James and Rempel. They found that aqueous acid solutions of some Rh(III) chloro complexes such as $[Rh(H_2O)Cl_5]^{2-}$ were able to promote the reaction



Scheme 6 Proposed mechanism for Rh catalyzed hydration of acetylene



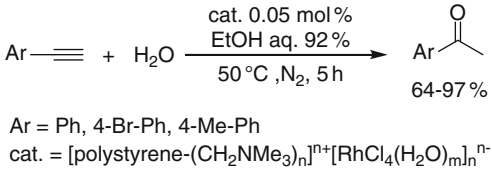
Scheme 7 $RhCl_3$/Aliquat 336® catalyzed hydration of alkynes

under mild conditions [17]. The kinetics and the mechanism were similar to that reported for a Ru(III) chloro system [18, 19] but the reaction demonstrated to run three times faster. Nevertheless, deactivation was a problem for this Rh(III) system. The proposed mechanism involved the presence of a water molecule as ligand on the Rh center and the formation of a π-complex of the metal with alkyne (Scheme 6). The coordinated water ligand is somewhat acidic. The acidity of a π-complex $[Rh(H_2O)Cl_4(C_2H_2)]^{2-}$ is likely to be greater than that of $[Rh(H_2O)Cl_5]^{2-}$, and the ionization probably occurs with the acetylene complex. Nucleophilic attack by the coordinated OH^- at the C atom finally yields the σ-complex, which is then decomposed by electrophilic attack by a proton at the C atom attached to the metal to regenerate the Rh(III) catalyst and give the hydration product.

A related study was reported in 1992 by Blum and Alper [20]. The authors showed that the ion pairs generated from $RhCl_3$ and a quaternary ammonium salt (Aliquat 336®) promoted the hydration of alkynes (Scheme 7).

They demonstrated that the catalytic species is the ion pair $[CH_3N(C_8H_{17})_3]^+[RhCl_4(H_2O)_2]^-$. The solvent of choice was THF, but haloalkanes were preferred when the recovery of rhodium was desired. The reaction on terminal alkynes was regiospecific yielding only the Markovnikov product. The quaternary ammonium ions seemed to act not only as a phase-transfer agent but also as essential part of the catalytic system. Unfortunately, due to the competitive cyclotrimerization process of alkynes, the yields are not good enough for preparative purposes. Some years later, the same group reported that polystyrene supported ion pairs generated from $RhCl_3$ and Dowex® 1 ion exchanger were able to efficiently hydrate aromatic terminal alkynes yielding selectively the corresponding Markovnikov product in good yields [21] (Scheme 8).

Unfortunately, under these conditions, aliphatic acetylenes proved to undergo only catalytic oligomerization.



Scheme 8 $RhCl_3$/Dowex® 1 catalyzed hydration of alkynes

3.1.2 Nitriles

In the literature, there are some examples of Rh(III) promoted hydrolysis of simple nitriles such as acetonitrile and benzonitrile. Ford and Zanella studied the base hydrolysis of some metal complexes of nitriles and found that the hydration of $Rh(NH_3)_5(N{\equiv}CCH_3)^{3+}$ was approximately 10^6 faster than the free acetonitrile but 10^2 times slower than the analogous Ru (III) complex [22]. The authors suggested that the hydrolysis rates are related to the acidities of metal centers and that such effects are function of both electronic and electrostatic factors [23]. On the other hand, the same system was studied by Sargeson and Curtis [24], who suggested that the addition of nucleophile is not the rate-determining step, and that the effect of polarization of the ligand by the metal ion is therefore obscured. More recently, Kukushkin and Isobe reported a novel type of metallocyclic dirhodium complex $[Rh_2Cp_2^*(\mu\text{-}CH_2)_2(\mu\text{-}O_2CO)]$ that readily hydrolyzes acetonitrile to give the corresponding amidato complex [25].

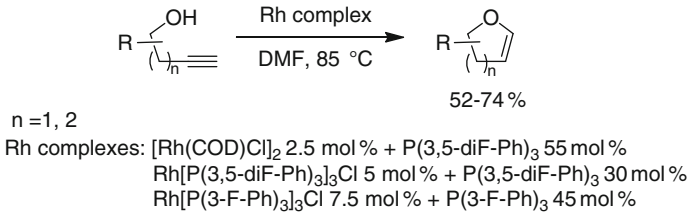
3.2 Hydroalkoxylation

3.2.1 Alkynes

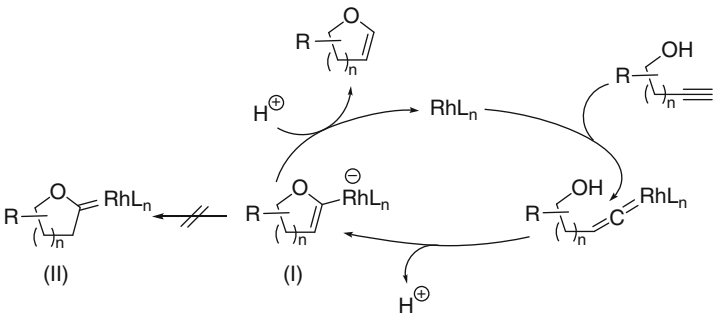
Based on the well-known ability of Rh to form vinylidene complexes from terminal alkynes [26, 27], Trost and Rhee tested a series of Rh(I) phosphine complexes as catalysts for the cycloisomerization of homo- and bis-homopropargylic alcohols to obtain dihydrofurans and dihydropyrans under neutral conditions [28] (Scheme 9).

Best results were obtained with $Rh(PR_3)_3Cl$ and $[Rh(COD)Cl]_2$ catalysts in the presence of an excess of electron-poor triaryl phosphines to avoid undesirable dimerization/oligomerization processes. The proposed reaction mechanism involves the formation of the Rh-vinylidene complex followed by the intramolecular *endo-dig* cyclization. The protodemetallation of intermediate **I** seems to be the more plausible path, whereas the formation of the Rh-oxacarbene complex **II** was excluded because all attempts to generate lactones by using N-hydroxysuccinimide failed and the cycloisomerization product was the only product obtained (Scheme 10).

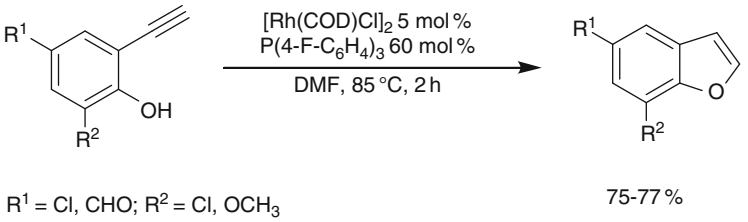
Four years later, within a more in-depth study on the Rh-catalyzed synthesis of indoles starting from *o*-alkynylanilines, the same group successfully extended this approach to the preparation of benzofurans starting from *o*-alkynylphenols [29].



Scheme 9 Rh(I) catalyzed cycloisomerization of homo- and bis-homopropargylic alcohols



Scheme 10 Proposed reaction mechanism for Rh(I) catalyzed cycloisomerization of alkynyl alcohols

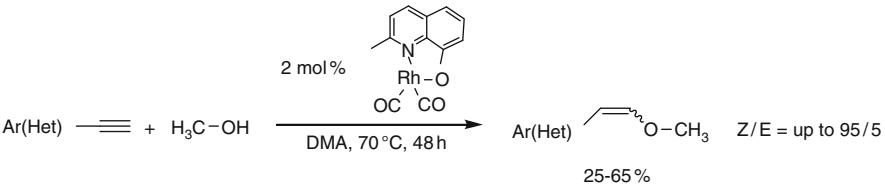


Scheme 11 Rh(I) catalyzed synthesis of benzofurans from *o*-alkynylphenols

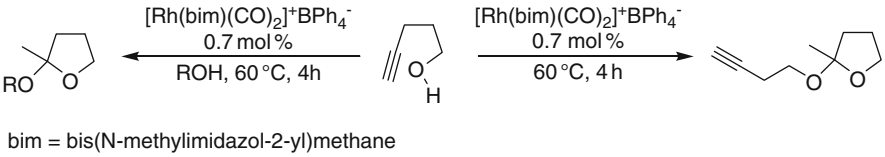
Also in this case, best results were obtained with 5 mol% $[Rh(COD)Cl]_2$ and an electron-poor triaryl phosphines in 60 mol% (Scheme 11).

The authors reported also one example that demonstrated the suitability of the method also for the synthesis of enol lactones starting from alkynyl carboxylic acids. Also in this case, due to the mechanism involving a Rh-vinylidene complex, the approach is limited to terminal alkynes.

An analogous mechanism that probably involves a Rh-vinylidene intermediate has been very recently proposed by Kakiuchi and coworkers in the first example of anti-Markovnikov intermolecular hydroalkoxylation of terminal acetylenes [30]. The approach gave enol ethers in good yields with a remarkable *Z*-stereoselectivity. The reaction between acetylenes and an excess of methanol gave best results in the



Scheme 12 Rh(I) catalyzed anti-Markovnikov intermolecular hydroalkoxylation of terminal acetylenes



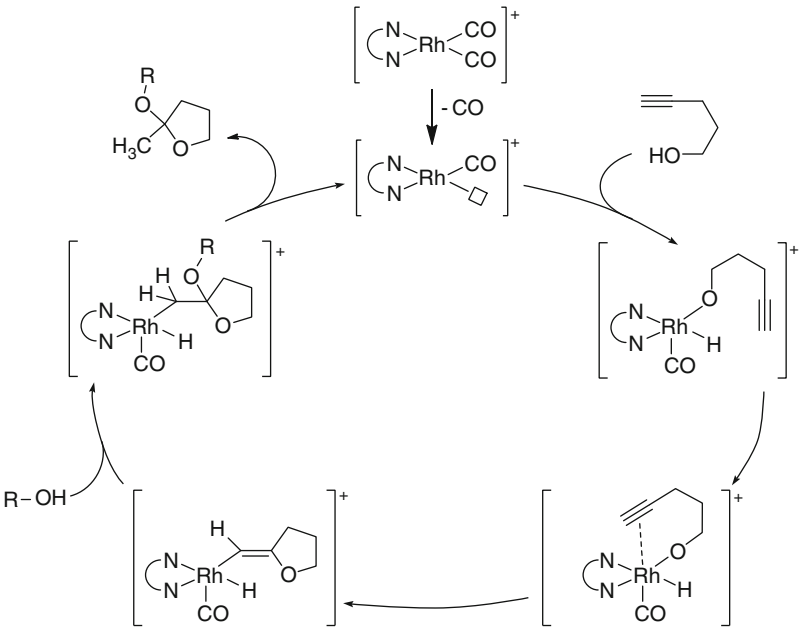
Scheme 13 Rh(I) catalyzed cyclization of alkynyl alcohols

presence of 2 mol% dicarbonyl(2-methyl-8-quinolinolato)rhodium in DMA at 70°C (Scheme 12).

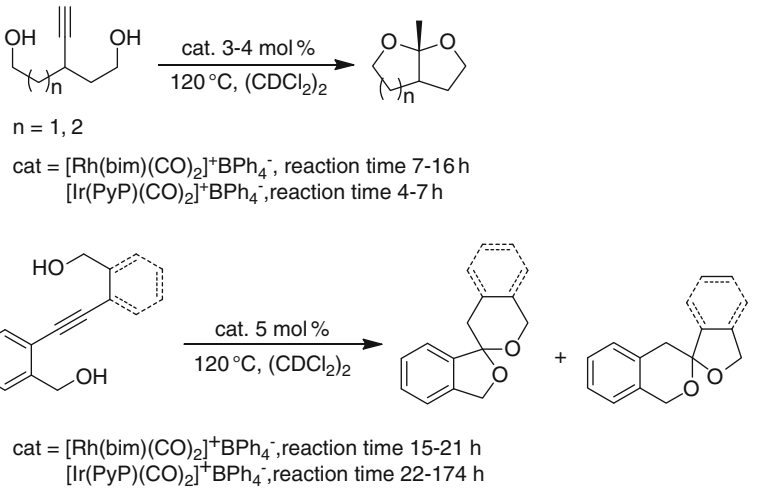
The hydroalkoxylation was catalyzed specifically by dicarbonyl (8-quinolinolato)rhodium complexes, in fact the substitution of a CO ligand with PPh_3 or both with COD ligand were unsuccessful. Simple Rh, Ir, and Ru carbonyl complexes were also ineffective. Aryl and heteroaryl acetylenes gave the best yields and selectivities, whereas the reactions of alkenyl and alkyl acetylenes gave unsatisfactory results. Also, the use of higher alcohols such as ethanol and *iso*-propanol was tolerated but increasing of catalyst loading and reaction times was necessary, whereas the reaction with phenols needed a catalytic amount of the weak base 2,6-lutidine, and gave modest yield and stereoselectivity.

The group of Messerle studied in depth the cationic Rh(I) catalyzed cyclization of alkynyl alcohols and alkynyl carboxylic acids. In 2000, they reported the cyclization of 4-pentynols to five-member cyclic acetals in which a molecule of alcohol (either from the solvent or from a second molecule of the starting alcohol) is incorporated into the products [31]. The reactions were performed in the presence of $[Rh(bim)(CO)_2]^+BPh_4^-$ (bim = bis(*N*-methylimidazol-2-yl)methane), in acetone-d_6 at 60°C in a nuclear magnetic resonance (NMR) tube (Scheme 13).

The cyclization did not work well with 4- or 6-carbon terminal alkynols or with compounds containing nonterminal alkynes. The proposed mechanism involved initial oxidative addition of the OH group to the rhodium center with loss of CO and coordination of the pendant acetylene. Migratory insertion in a 5-*exo-dig* mode produces the coordinated cyclic vinyl ether, which could add an alcohol to the vinyl group and reductive elimination of the organic product regenerates the reactive metal complex. Alternatively, reductive elimination from the metal vinyl ether would produce a vinyl ether, which would be trapped by the alcoholic solvent (Scheme 14).



Scheme 14 Proposed mechanism for Rh(I) catalyzed cyclization of alkynyl alcohols



Scheme 15 Rh(I) catalyzed double intramolecular hydroalkoxylation of alkynediols

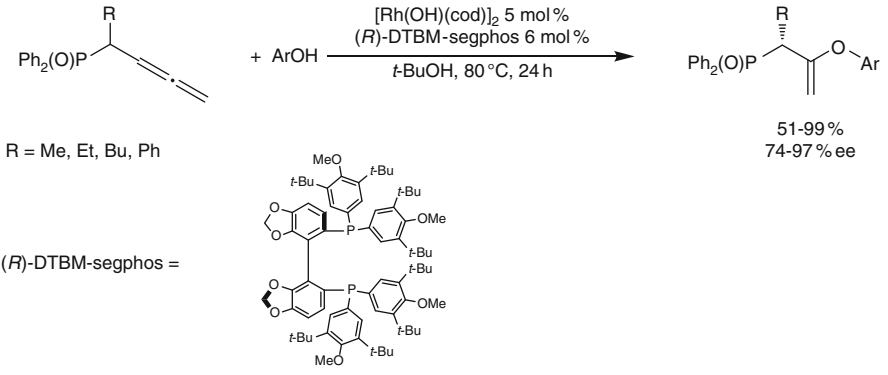
The same catalyst was used for the double intramolecular hydroalkoxylation reaction for the synthesis of a series of spiroacetals starting from internal and terminal alkynediols [32] (Scheme 15).

The efficiency of the rhodium catalyst was compared with that of the iridium complex $[Ir(PyP)(CO)_2]BPh_4$ (PyP = 1-[2-(diphenylphosphino)ethyl]pyrazole). The latter resulted more effective for the cyclization of aliphatic substrates, whereas the Rh-complex was significantly more efficient in the reaction of aromatic substrates. The mechanism was studied by low-temperature NMR spectroscopy and deuteration experiments. Unlike what is reported in their previous work [31], the authors postulate an alternative catalytic cycle in which the initial step of the reaction cycle involves the association of the alkyne with the metal center, but unfortunately the mechanistic studies were done only on the Ir-complex.

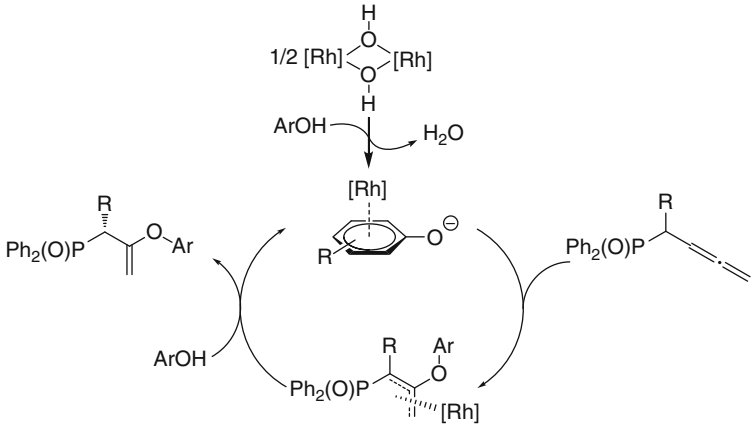
The synthesis of spiroacetals was improved by using new simple and readily accessible $Rh(COD)_2$ complexes that allowed excellent conversions and an overall reduction of reaction times [33]. Moreover, very recently a dual metal catalytic system (Rh(I) and Ir(I)) was successfully utilized for these reactions on alkynediols, and in some cases it works more efficiently than the single metal catalyst [34]. The combination of the two metal complexes ($[Rh(bpm)(CO)_2]BAr_4^F$ and $[Ir(bpm)(CO)_2]BAr_4^F$ (bpm = bis(1-pyrazolyl)methane, BAr_4^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) acted cooperatively to promote an efficient dual activation pathway for both the 5-*exo* and 6-*endo* cyclization in which the Rh(I) preferentially promotes the 6-membered ring formation, while the Ir(I) in preference promotes the 5-membered cyclization of alkynediols.

3.2.2 Allenes

Only recently, an example of rhodium-catalyzed allene hydroalkoxylation has been reported by Nishimura, Haysashi, and coworkers [35]. The asymmetric addition of phenols to diphenylphosphinylallenes was achieved in high yields and ee in the presence of the hydroxorhodium complex $[Rh(OH)(cod)]_2$ coordinated with the hindered chiral bisphosphine ligand (*R*)-DTBM-segphos in *tert*-butyl alcohol (Scheme 16).



Scheme 16 Rh(I) catalyzed hydroalkoxylation of allenes



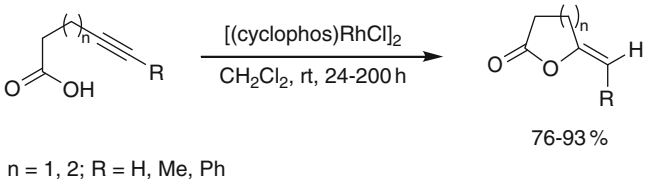
Scheme 17 Proposed mechanism for Rh(I) catalyzed hydroalkoxylation of allenes

The allene/phenol ratio had a significant influence on the enantioselectivity; best results were obtained with a 2:1 ratio. Ortho-substituents and electron-withdrawing groups on the phenol increased the enantioselectivity. The reaction of allenes substituted with Et, Bu, and Ph groups also took place to give the corresponding vinyl ethers, the enantioselectivity being lower with more bulky substituents. The mechanism was carefully investigated by means of ^{1}H and ^{31}P NMR studies and involved two different Rh-complexes. First, treatment of the catalyst with phenol brought about the selective formation of a π-phenoxorhodium complex, after that when the allene was added a new π-allylrhodium was observed. Finally, protonolysis of the π -allylrhodium with phenol gave the hydroalkoxylation product, regenerating phenoxorhodium complex (Scheme 17).

3.3 Hydroacyloxylation

3.3.1 Alkynes

The chemistry of hydroacyloxylation (also called hydrooxycarbonylation) of alkynes is dominated by intramolecular reaction to form enol lactones bearing exocyclic double bonds. In 1987, Chan, Marder, and coworkers designed a new specific Rh-catalyst for the intramolecular addition of carboxylic acid to alkynes [36, 37]. The catalytic system was designed taking into account that electron-rich metal complex could activate the acid moiety via oxidative addition, and the intermediate should cyclize because the oxidized metal could act as a Lewis acid. Thus, high regioselective lactonizations were accomplished in the presence of



Scheme 18 Rh(I) catalyzed intramolecular addition of carboxylic acid to alkynes

$[(cyclophos)RhCl]_2$ (cyclophos = 1,2-bis(dicyclohexylphosphino)ethane) under mild conditions in high yields (Scheme 18).

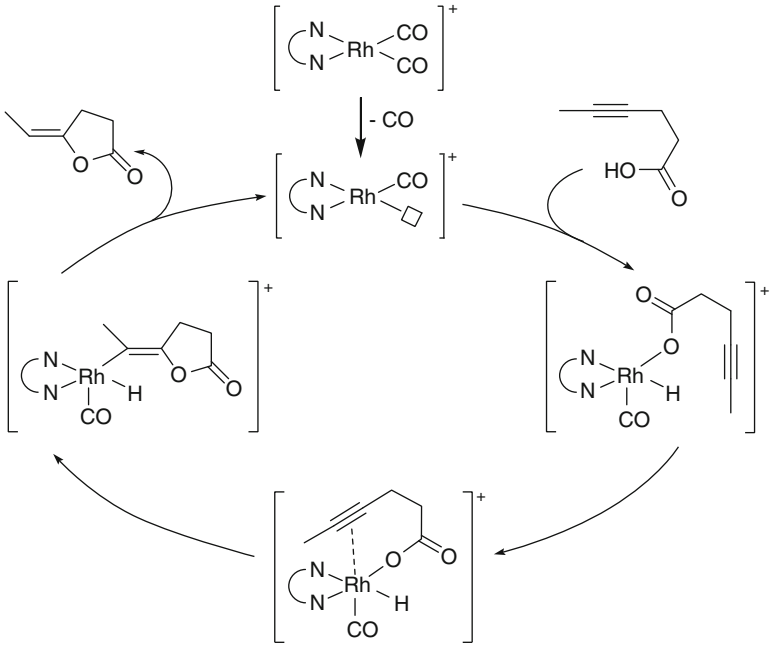
The catalyst showed superior activity when compared to other transition-metal complexes or Hg salts. Starting from internal alkynes, exclusive *Z* stereochemistry was observed in the product, due to a selective *trans*-addition of the carboxylate to the alkyne. When the size of the substituent on the acetylenic moiety was increased, a strong reduction of reaction rate was observed indicating that the coordination of the triple bond to the metal center plays a pivotal role in cyclization. The proposed mechanism involves the initial OH activation by the low-valent metal complex, followed by nucleophilic attack of the carboxylate on the coordinated acetylene and finally by the reductive elimination to give the lactone and regenerate the catalyst as shown in Scheme 3.

Similar results were obtained by Messerle, Field, and coworkers using the cationic Rh-complex $[Rh(bim)(CO)_2]BPh_4$ (bim = bis(*N*-methylimidazol-2-yl) methane) in acetone-d_6, at 50°C [31]. The advantages of this catalyst with respect to $[(cyclophos)RhCl]_2$ [36, 37] were lower catalyst loading (0.35–0.7 vs 2.0 mol%), and shorter reaction times (i.e., 15.5 vs 24 h). Conversely, the temperature required was higher and the yield for cyclization of internal 4-hexynoic acid was poorer (26 vs 79 %). In contrast with that observed by Chan and Marder, the cyclization of the latter resulted in the exclusive formation of the *E*-isomer. This suggested a mechanism in which the carboxylate was not lost from the metal prior to attack on the alkyne and the migratory insertion delivers the oxygen to the coordinated triple bond from metal center, ensuring the *E*-stereochemistry in the product (Scheme 19).

4 Iridium

The major reason why the development of iridium-catalyzed reactions is far behind that of rhodium-, palladium-, and platinum-catalyzed reactions is connected to the high stability of the iridium complexes.

A breakthrough in the study of iridium-catalyzed reactions was reported by Crabtree in 1977 regarding the hydrogenation reactions of alkenes [38, 39]. Only recently, iridium complexes have been utilized on alkynes for other reactions than the hydrogenation.



Scheme 19 Proposed mechanism for Rh(I) catalyzed intramolecular addition of carboxylic acid to alkynes

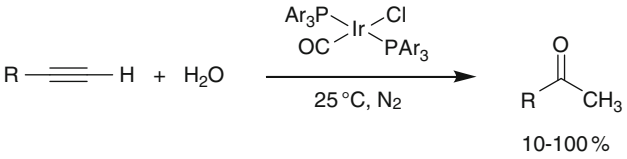
4.1 Hydration

4.1.1 Alkynes

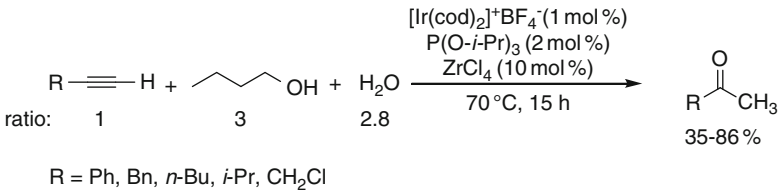
The hydration of alkynes with water-soluble iridium complexes was studied in detail for the first time by Chin and coworkers. In particular, $(TPPTS)_2(CO)IrCl{\cdot}H_2O$ (TPPS = *m*-trisulfonated triphenylphosphine) was found to catalyze the hydration of terminal alkynes to give ketones at room temperature and in MeOH as solvent (900 turnovers). The hydration did not occur in the presence of TPPTS only and occurred very slowly in the presence of other water soluble complexes. The hydration of acetylene was much faster than those of terminal alkynes probably due to steric hindrance, whereas internal alkynes did not react at all [40] (Scheme 20).

The addition of water in the presence of alcohols to nonactivated terminal alkynes to give ketones was promoted also by the precursor complex $[Ir(cod)_2]BF_4$, in combination with $ZrCl_4$ or other chloride containing Lewis acids and P(O*i*-Pr)$_3$ as co-ligand [41]. The reaction in the absence of alcohol resulted in low yield; this may suggest that the reaction proceeded through the formation of a ketal followed by hydrolysis with water (Scheme 21).

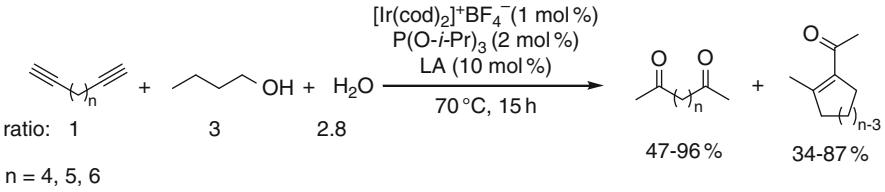
The reaction of α,ω-diynes with water afforded cyclized carbonyl derivatives in good yields (Scheme 22). The formation of cyclic carbonyl compound was



Scheme 20 Hydration of alkynes



Scheme 21 Hydration of alkynes in presence of alcohols

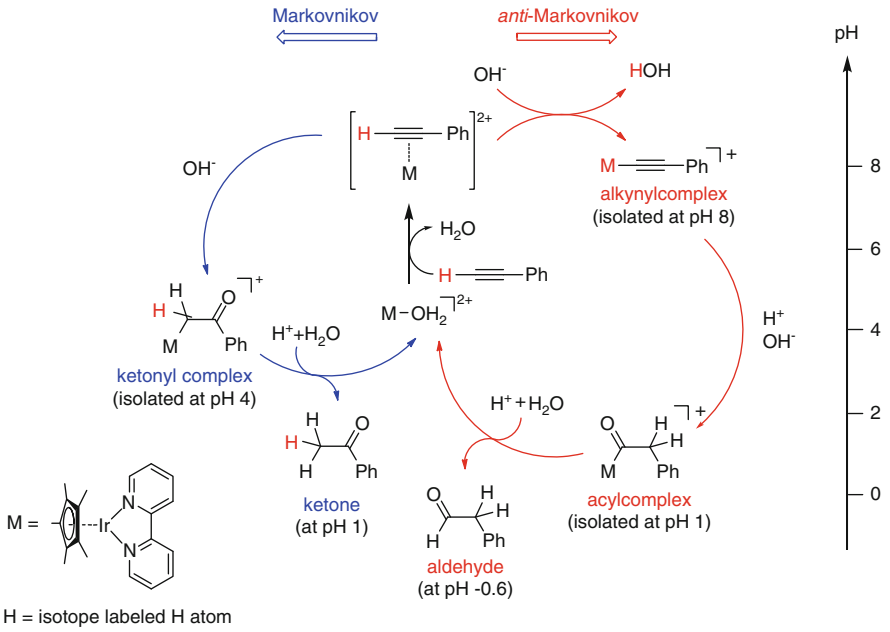


Scheme 22 Hydration of α,ω-diynes

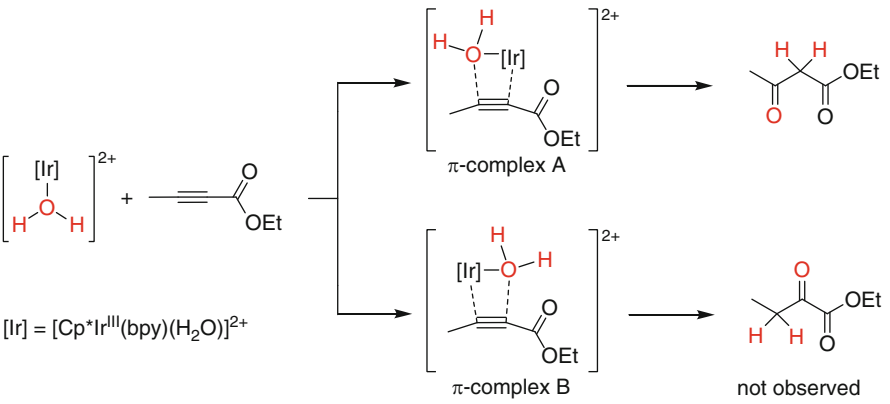
rationalized by assuming the intramolecular aldol condensation of the dione obtained by Lewis acid catalysis during the reaction. Alternatively, in the case of too large rings, diketones were isolated.

A valuable insight into the regioselective hydration of a terminal alkynes was provided by isolation of different intermediate complexes, depending on the pH of the solution, as shown in Scheme 23. By starting from the same water-soluble iridium(III) aqua complex $[Cp^*Ir^{III}(bpy)(H_2O)]^{2+}$ ($Cp^* = \eta^5$-C_5Me_5, bpy = 2, 2′-bipyridine), at pH 8 the alkynyl intermediate $[Cp^*Ir^{III}(bpy)CCPh]^+$ was synthesized; by changing the pH of the aqueous solution from 8 to 1, the acyl intermediate $[Cp^*Ir^{III}(bpy)C(O)CH_2Ph]^+$ was formed giving the aldehyde as result of the anti-Markovnikov hydration. The ketonyl intermediate isolated at pH 4 gave Markovnikov hydration with the formation of the ketone [42].

Further elucidations on the mechanism of alkynes hydration arise from the isolation of both enol and keto tautomers of organometallic intermediates, starting from an alkyne-carboxylic acid ester as tetrolic acid ethyl ester [43].



Scheme 23 Mechanism of alkynes hydration



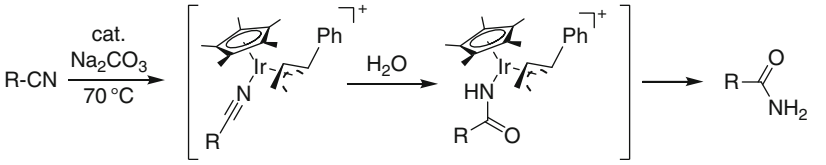
Scheme 24 Regioselectivity in tetrolic acid ethyl ester hydration

The Ir-complex $[Cp^*Ir^{III}(bpy)(H_2O)]^{2+}$ (**1**) catalyzes the *syn* addition of the H_2O ligand of Ir-aqua complex **1** into the carbon–carbon triple bond. It can be assumed that the π-complex **A** is formed between the two possibilities because the product of the hydration is ethyl acetoacetate but not ethyl 2-oxobutanoate (Scheme 24).

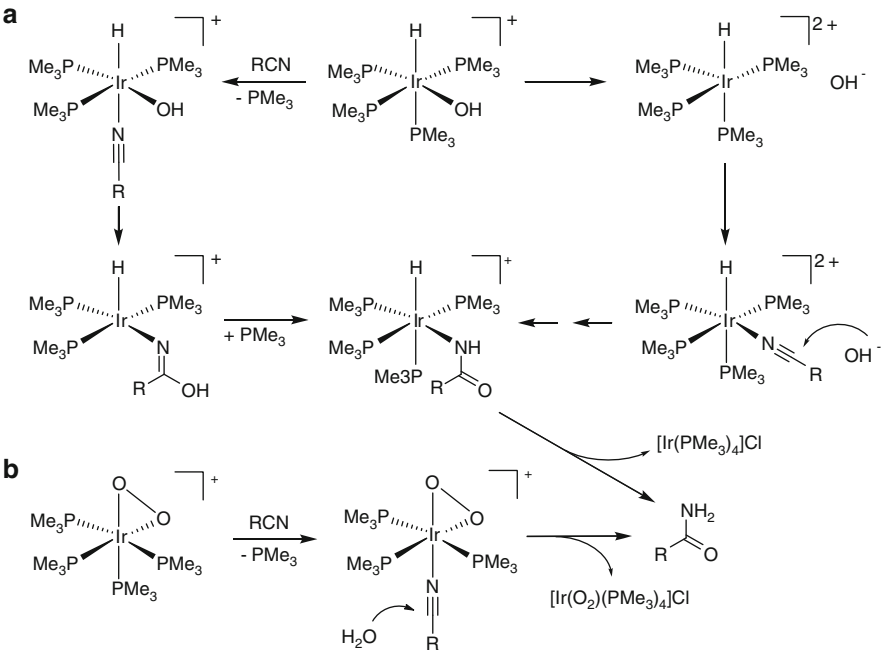
4.1.2 Nitriles

Nitrile complexes [Cp*Ir(η^3-$CH_2CHCHPh$)(NCMe)]OTf (Cp* = C_5Me_5- and OTf = $-OSO_2CF_3$) and [Cp*Ir(η^3-$CH_2CHCHPh$)(NCCH = CHMe)]OTf catalyzed the hydration of the nitriles (acetonitrile, crotononitrile, benzonitrile) in the presence of Na_2CO_3 to produce amides. Plausible mechanism for these catalytic reactions involved the amido-ether complex formation [44]. Also, unsaturated nitriles were treated under these catalytic conditions [45] (Scheme 25).

More recently, the iridium complexes $[Ir(PMe_3)_4]Cl$, as well as the more electrophilic peroxo derivative $[Ir(O_2)(PMe_3)_4]Cl$, were catalyst precursors for a variety of nitriles RCN (R = Me, *p*-$NH_2C_6H_4$, *p*-OHC_6H_4) giving up to 800 turnovers in the hydration reaction realized at 140°C. Various general mechanisms for the hydration of nitriles are possible, two of which involve insertion into a metal-hydroxo bond (Scheme 26a) or nucleophilic attack of water upon coordination of



Scheme 25 Nitriles hydration



Scheme 26 Mechanisms proposed for nitriles hydration

the nitrile group (Scheme 26b). The activity of the iridium catalyst is comparable to those of nickel, ruthenium, palladium, and platinum systems using phosphines as auxiliary ligands [46].

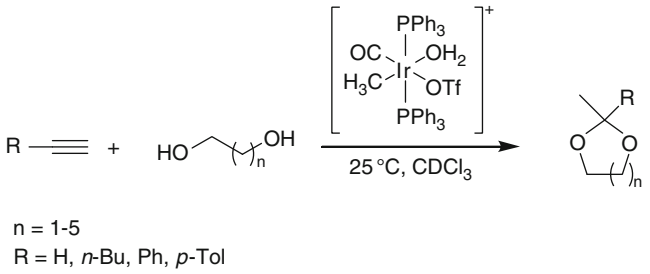
4.2 Hydroalkoxylation

4.2.1 Alkynes

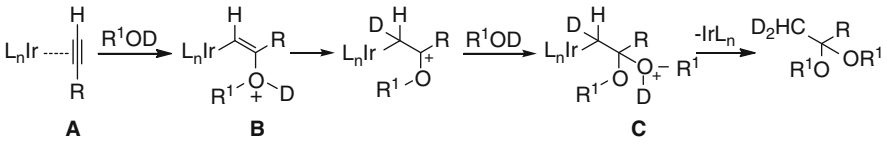
Cyclic acetals were produced from terminal alkynes and α,ω diols with cationic iridium(III) complex $[Ir(CH_3)(OTf)(CO)(H_2O)(PPh_3)_2](OTf)$, exclusively in the absence of water at room temperature. Whereas direct catalytic hydration of the alkynes was not possible, the cyclic acetals were hydrolyzed separately to methyl ketones [47] (Scheme 27).

A plausible mechanism involved a η^2-alkyne complex **A**, which was attacked by alcohol to give a β-alkoxy-alkenyl complex **B**. Proton transfer and attack by another alcohol molecule produced intermediate **C** that finally yielded the acetal (Scheme 28). It has been found that bulky substituents on alkynes caused a decrease in the rate of diol addition.

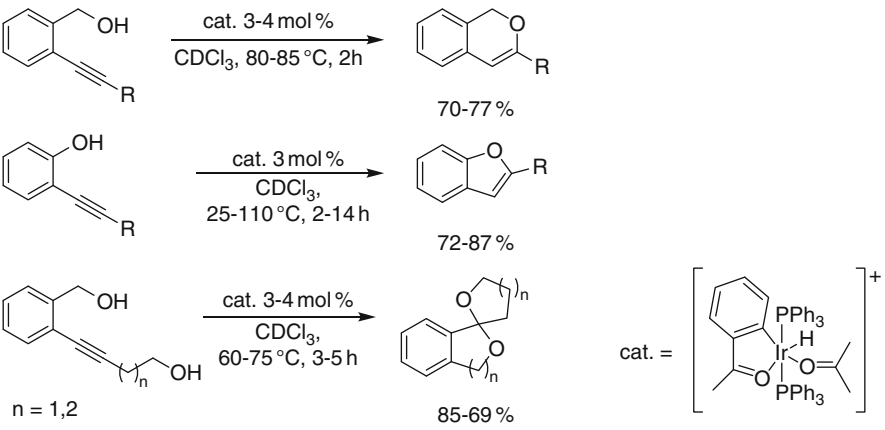
Intramolecular hydroalkoxylation of internal alkynes containing proximate oxygen nucleophiles was catalyzed by iridium hydride complex [48] (Scheme 29). The cyclization of 2-alkynylbenzyl alcohols follows highly selective 6-*endo-dig* regiochemistry for both alkyl and aryl substituents on the multiple bond. Cyclization of substrates having two OH groups gave spiroacetal derivatives. When



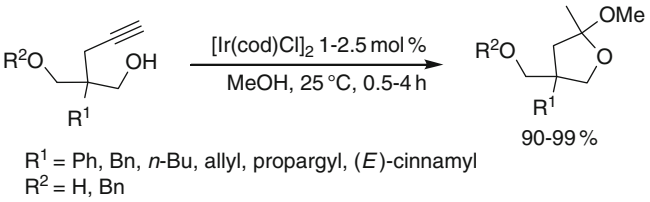
Scheme 27 Alkynes hydroalkoxylation



Scheme 28 Mechanism of alkynes hydroalkoxylation



Scheme 29 Intramolecular hydroalkoxylation



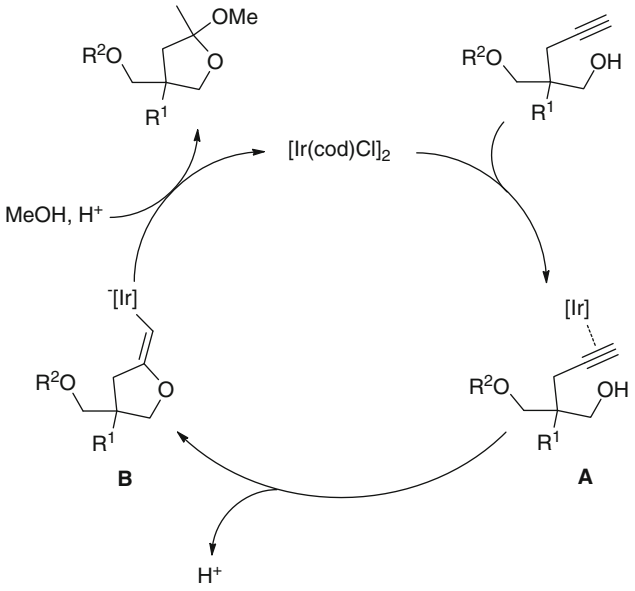
Scheme 30 Inter-intramolecular hydroalkoxylation

the same substrates are treated under Pd catalysis, the regioselectivity is dependent on the reaction conditions, in particular depending on the solvent used [49].

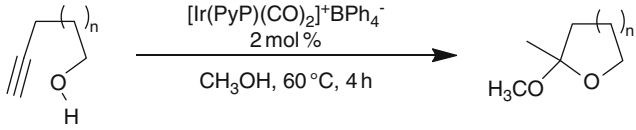
An efficient and interesting route for the construction of useful building blocks, furanyl and pyranyl derivatives, was developed starting from bis-homopropargylic alcohols. The $[Ir(cod)Cl]_2$ dimer complex was used for the first time to promote a tandem cyclization/hydroalkoxylation reaction, with total 5-*exo*-selectivity [50] (Scheme 30).

The proposed reaction mechanism may be initiated by the formation of the π-alkynyl complex **A** by the complexation of the unsaturated triple bond to the Ir (I) catalyst. Subsequent addition of the alcohol, which was supposed to occur anti to the π-complex **A**, would lead to a σ−complex **B**, which is favored in polar protic solvents such as MeOH, through a transient zwitterionic intermediate. Proton transfer may then be followed by the intermolecular addition of MeOH to give the cyclic ketal (Scheme 31).

The Ir-complex $[Ir(PyP)(CO)_2]BPh_4$ (PyP = 1-[2-(diphenylphosphino) ethyl] pyrazole) also led to products resulting from an *exo-dig* intramolecular cyclization of alkynols in the presence of an excess of methanol to form cyclic acetals [51] (Scheme 32).



Scheme 31 Mechanism of inter-intramolecular hydroalkoxylation



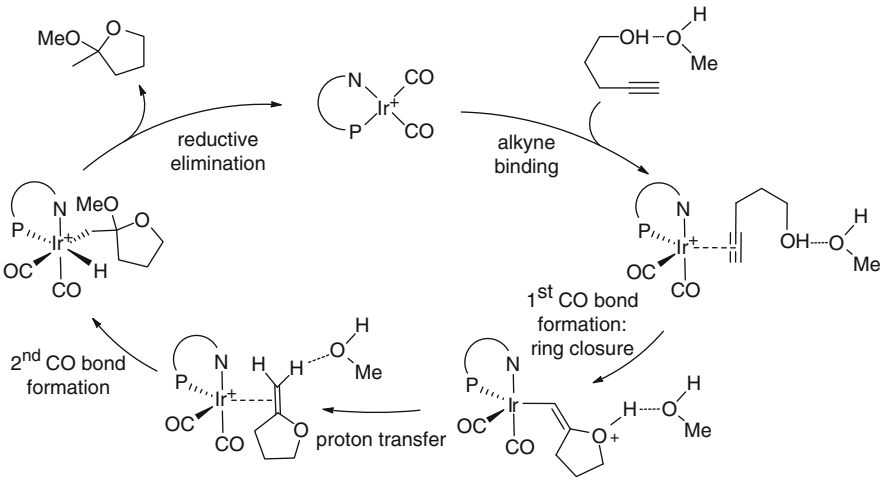
n = 1, 2

Py = 1-[(2-diphenylphosphino)ethyl]pyrazole

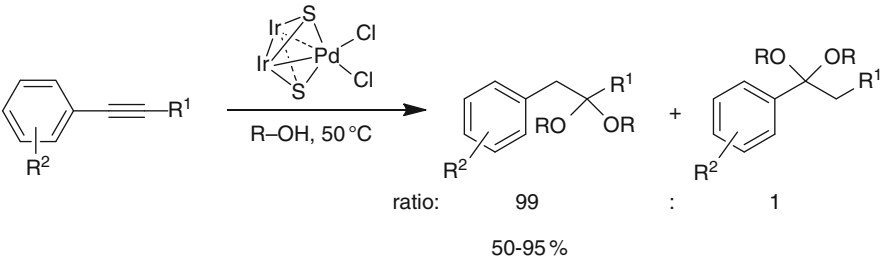
Scheme 32 Cyclic acetals formation

Mechanistic investigations showed that the catalytic cycle proceeded via π coordination of the alkyne to the metal center followed by the sequential addition of two hydroxyl groups to form *O,O*-acetals. Very recent computational study showed the key C–O bond forming cyclization step is greatly facilitated by the presence of an external H–bonded MeOH molecule that stabilizes the positive charge that develops at the hydroxyl proton of the bound alkyne [52] (Scheme 33).

The efficiency of a series of rhodium and iridium complexes as catalysts for the cyclization of terminal and nonterminal alkynes to give *O,O*-acetals and spiroketals was tested using $[Ir(PyP)(CO)_2]BPh_4$ and $[Rh(bim)(CO)_2]BPh_4$ (bim = bis (N-methylimidazol-2-yl)-methane [32–34]. The iridium complex was more efficient than rhodium in promoting the reactions of aliphatic alkyne diols. The rhodium was more effective for promoting the reactions of aromatic substrates (Scheme 15).



Scheme 33 Mechanism for cyclic acetals formation



Scheme 34 Heterobimetallic cluster catalyst for hydroalkoxylation of alkynes

A particular question was regarding the catalytic activity of the clusters. Their use in catalytic organic synthesis has not yet been explored extensively, although multinuclear complexes with sulfur-based ligands are of special interest for industrial processes considering the strong bridging ability of sulfur ligands to prevent fragmentation of the multimetallic cores and several efforts have been devoted to the synthesis of multinuclear transition-metal sulfur complexes.

If $PdMo_3S_4$ cubane-type cluster showed excellent catalytic activity for the stereoselective addition of alcohols [53] or carboxylic acids [54, 55] to electron-deficient alkynes, it failed with unactivated alkynes.

Hidai group studied multinuclear complexes of groups 8–10 noble metals with bridging sulfur ligands [56, 57]. The heterobimetallic cluster of Ir_2Pd catalyzed the addition of alcohols to nonactivated alkynes to give the corresponding acetals. The 1-aryl-1-alkynes with methanol were transformed into the corresponding 2,2-dialkoxy-1-arylalkanes with high regioselectivity up to 99:1 (Scheme 34). No other products such as enol ethers and ketones were detected. Since neither

monometallic palladium complexes with sulfur donor ligands nor iridium complexes were effective, the authors are inclined to believe that the catalysis was performed by the Ir_2Pd cluster whose core structure is retained during the reaction. Interestingly, the cluster can be recovered in 85% yield after the catalytic reaction. On the contrary, the Ir_2Pt cluster displayed good catalytic activity for the addition reaction, but the regioselectivity was much lower than that of Ir_2Pd.

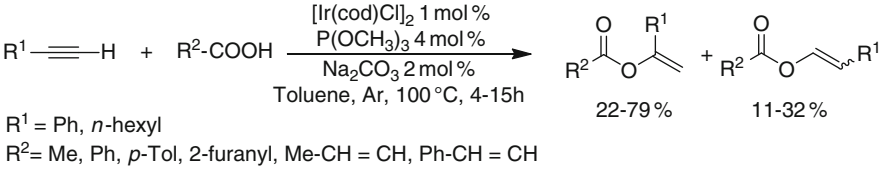
4.3 Hydroacyloxylation

4.3.1 Alkynes

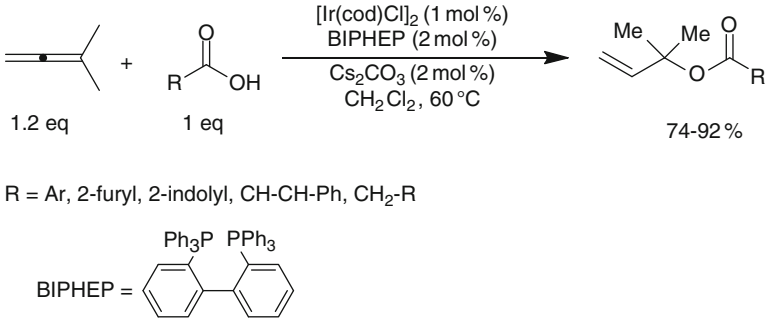
Enol and vinyl esters were successfully obtained starting from aliphatic and aromatic carboxylic acids with terminal alkynes, 1-hexyne or phenylacetylene. The addition reaction took place principally in the Markovnikov fashion to give 1-alkenyl esters, and it was facilitated by the use of catalytic amounts of $[Ir(cod)Cl]_2$ combined with small amounts of $P(OMe)_3$ and Na_2CO_3 [48, 58] (Scheme 35).

4.3.2 Allenes

Regioselective hydroacyloxylation of 1,1-dimethylallene with carboxylic acids exploiting iridium catalyst to prenyl ester was reported in 74–82% isolated yield [59] (Scheme 36).



Scheme 35 Alkynes hydroacyloxylation



Scheme 36 Allenes hydroacyloxylation

5 Nickel

Nickel catalyzed O–H additions to unsaturated systems are limited to the hydration reactions of nitriles for the synthesis of amides. These reactions have been widely studied by Prof. J. J. García and his research group and their results recently reviewed [60]. They reported the isolation and characterization of Ni(0) complexes of type [(dippe)Ni(η^2-NCR], R = aryl, heteroaryl or alkyl, derived from the reductive interaction of $[(dippe)NiH]_2$ with organic cyanides. The catalytic and synthetic utility of these complexes was demonstrated first in the catalytic hydration of benzonitrile and acetonitrile [61] and then extended to dicyanobenzenes [62], to mono- and dicyanoalkanes [63] and finally to cyanopyridines [64].

6 Palladium

Palladium is still the most used transition metal for catalytic addition of oxygen nucleophiles toward alkenes and alkynes, and this reactivity is one of the fundamental pathways in the organic reaction promoted by palladium.

6.1 Hydration

The Wacker process, an oxidative addition reaction, performed with Pd(II)-catalyst in the presence of an oxidant is out of scope of this review. Nevertheless, some representative references concerning Wacker reaction are given [65–72].

6.1.1 Alkenes

The hydration of C–C multiple bonds is a reaction with prevalent industrial interest due to the usefulness of the products as chemical intermediates. The wool-Pd complex is an economical and highly active catalyst for hydration of olefins. It is very stable and can be reused several times without any remarkable change in the catalytic activity [73, 74]. In particular, to convert alkenes to the corresponding alcohols in excellent enantioselectivity, a new biopolymer-metal complex constituted of wool-supported palladium-iron or palladium-cobalt was prepared and used, such as allylamine to amino-2-propanol, acrylonitrile to lactonitrile and unsaturated acids to α-hydroxycarboxylic acids [75–77]. The same catalytic system was also used for hydration of substituted styrenes to produce chiral benzyl alcohols. The simple and cleaner procedure, mild reaction conditions, high stability and recovery rate of catalyst made these catalytic systems an attractive and useful alternative to the existing methods (Scheme 37).

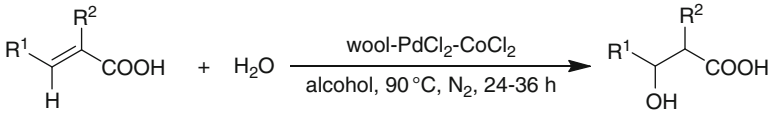
6.1.2 Alkynes

The ketones resulting from the hydration of alkynes are useful chemical intermediates. For these reasons, attempts to develop nonmercury alkyne hydration were pursued. The system Nafion(Pd^{2+}) resin catalyst was the first reported to be active for the hydration of alkynes, including α-hydroxy alkynes, giving in high selectivity α-hydroxy-ketones [78]. At the same time, Cacchi and coworkers described the Pd(II)-catalyzed hydration of enynes as key-step involved in a sequential process starting from vinyl triflates and affording γ-hydroxy-α, β-enones [79].

6.1.3 Nitriles

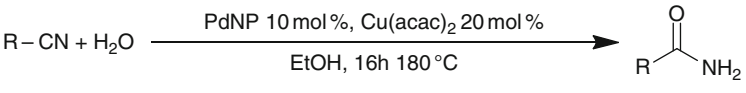
A new catalytic system based on Pd nanoparticles for the hydration of various nitriles to amides was investigated. Copper compounds containing oxygen acted as effective promoters in the catalytic system. Chloride ions significantly inhibited the catalytic performance [80] (Scheme 38).

An efficient palladium-catalyzed protocol for the hydration of alkyl and aryl nitriles to amides has been disclosed, employing acetaldoxime as efficient water delivering surrogate to nitrile. A plausible mechanism was suggested involving Pd(II)-catalyzed nitrile–oxime coupling followed by disruption of the intermediate into benzamide and acetonitrile in a concerted manner [81–83] (Scheme 39).



R^1 = H, Me, COOH; R^2 = H, Me

Scheme 37 Alkenes hydration



R = Ph, Pr, $BnCH_2$, 2-py, 4-MeOPh

Scheme 38 Nitriles hydration

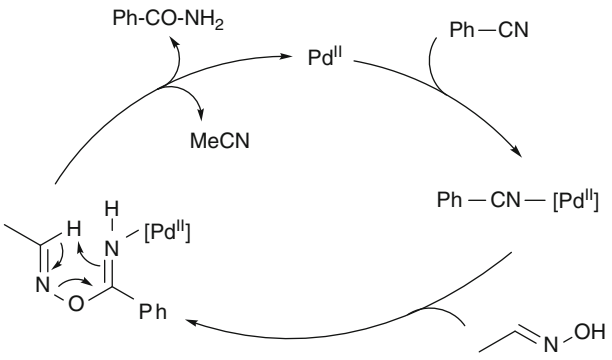
6.2 *Hydroalkoxylation*

6.2.1 Alkenes

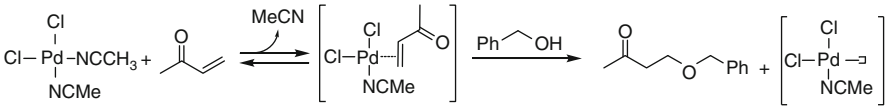
In connection with the interest on the hydroalkoxylation of terminal alkenes bearing electron-withdrawing substituents [84, 85], the kinetic and mechanism of alcohols addition to MVK using $PdCl_2(CH_3CN)_2$ has been investigated in detail, showing selective addition to the β-carbon, with formation of the anti-Markovnikov product. The most consistent mechanism involved substitution of an acetonitrile ligand by MVK in a preequilibrium step followed by nucleophilic attack of alcohol. The reaction was sensitive to steric hindrance of the alcoholic nucleophile: 1> 2 > 3 [86] (Scheme 40).

The same catalyst was used in anhydrous THF at room temperature for the tetrahydropyranylation of primary alcohols in the presence of various functional groups as phenols, secondary and tertiary alcohols. The protecting group could be efficiently removed in CH_3CN using the same catalyst while other protection groups remained intact under these conditions [87] (Scheme 41).

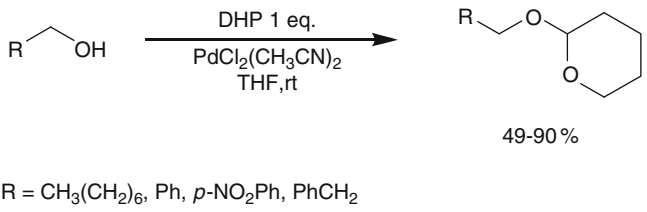
Intermolecular hydroalkoxylation of vinylphenols has been developed by Sigman using Pd(II) and primary, secondary or tertiary alcohols. The key breakthrough was the use of *sec*-phenetyl alcohol as the sacrificial reagent as the hydride source promoting the formation of Pd-H intermediate. The subsequent olefin insertion, the formation of an *o*-quinone methide intermediate and the addition of



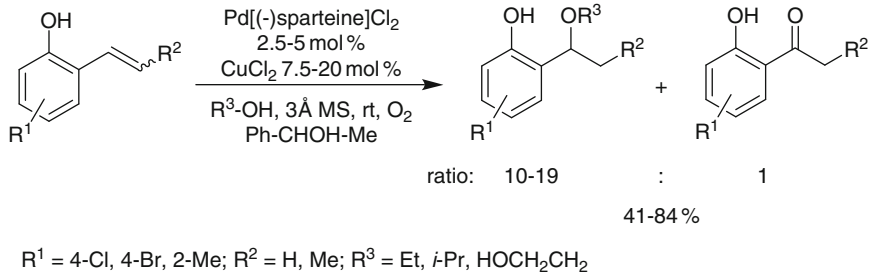
Scheme 39 Mechanism of nitriles hydration

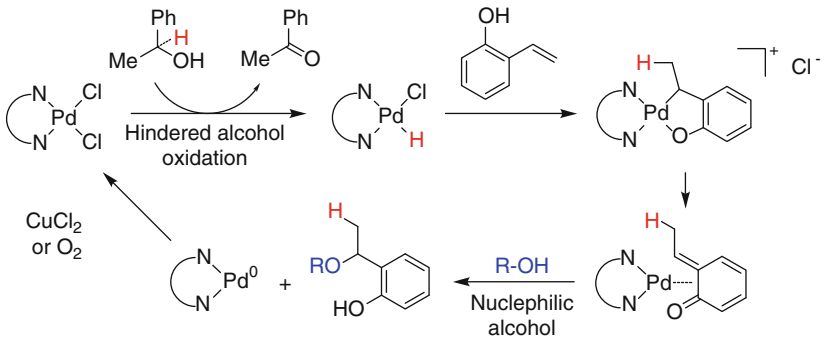


Scheme 40 Alcohol addition to MVK



Scheme 41 Tetrahydropyranylation of primary alcohols



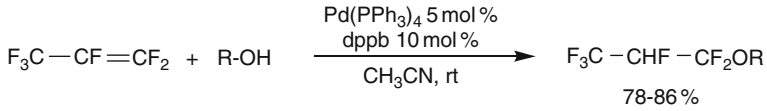


Scheme 42 Hydroalkoxylation of vinyl phenols

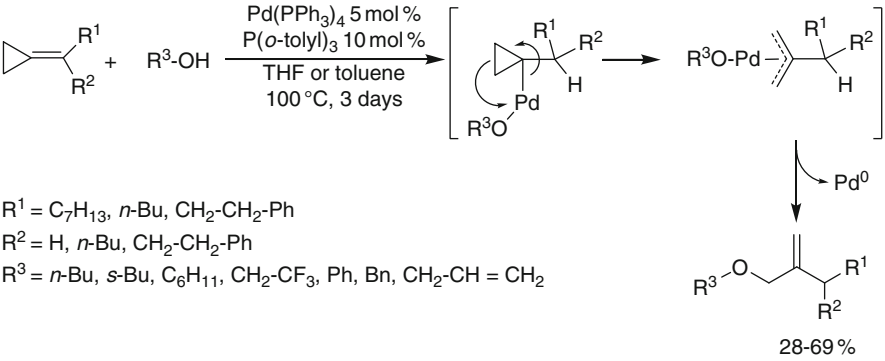
a second equivalent of the alcohol to the *o*-quinone methide leads to product formation [88, 89] (Scheme 42).

The first synthesis of saturated hydrofluoroethers was realized in 2005, through the addition of various alcohols to a fluorinated alkene in the presence of $Pd(PPh_3)_4$ under neutral conditions, at room temperature. With poor acidic alcohols, catalytic activity was increased in the presence of cocatalytic 1,4-bis-(diphenylphosphino) butane (dppb) [90] (Scheme 43).

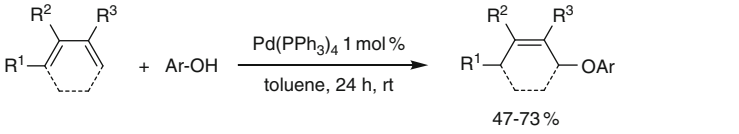
Methylenecyclopropanes were particular substrates object of several studies by Yamamoto [91]. The interest in the addition of alcohols was due to the formation of allyl ethers with high regioselectivity, through the distal bond cyclopropane cleavage of the hydropalladate intermediate as shown in Scheme 44. Combination of Pd



Scheme 43 Hydroalkoxylation of fluorinated alkene



Scheme 44 Hydroalkoxylation of methylenecyclopropanes

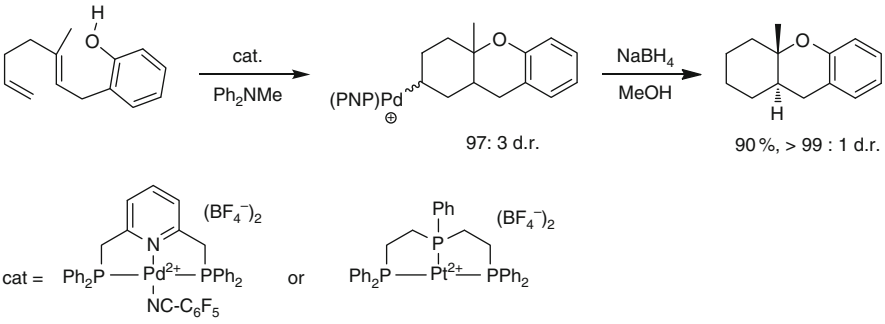


Scheme 45 Addition of phenols to dienes

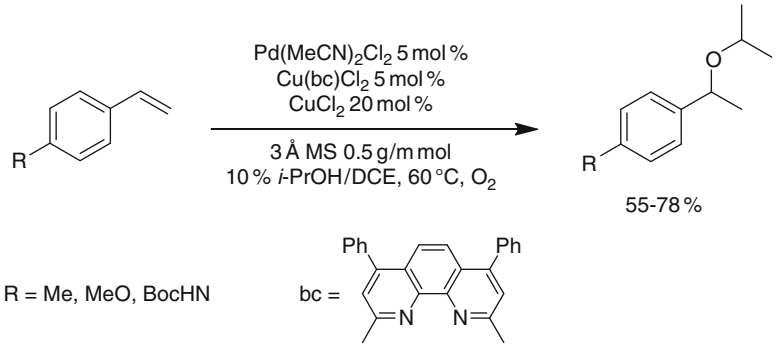
$(PPh_3)_4$ and P(*o*-tol)$_3$ was the best catalytic system [92]. The proposed mechanism is in accordance with the sequence showed for other alkene substrates.

The addition reaction of phenols across cyclic and acyclic dienes with $Pd(PPh_3)_4$ occurred at room temperature without cocatalyst to give allyl aryl ethers in good yields [93] (Scheme 45). Similarly, carboxylic acids react with dienes affording allyl esters.

An electrophilic Pd(II) source, the dicationic pincer complex $Pd(PNP)(BF_4)_2$ (PNP = 2,6-bis(diphenylphosphanylmethyl)pyridine), was exploited in a cascade polycyclization of 1,5- and 1,6-dienes bearing an –OH nucleophile to give polycyclic systems. The diastereoselectivity was consistent with the hypothesis of a cationic intermediate [94]. The stability of the metal species intermediate prevented β-elimination. Similar result was obtained with a Pt dicationic pincer complex (Scheme 46) [95].



Scheme 46 Pincer Pd-complex for cascade polycyclization of 1,5-dienes



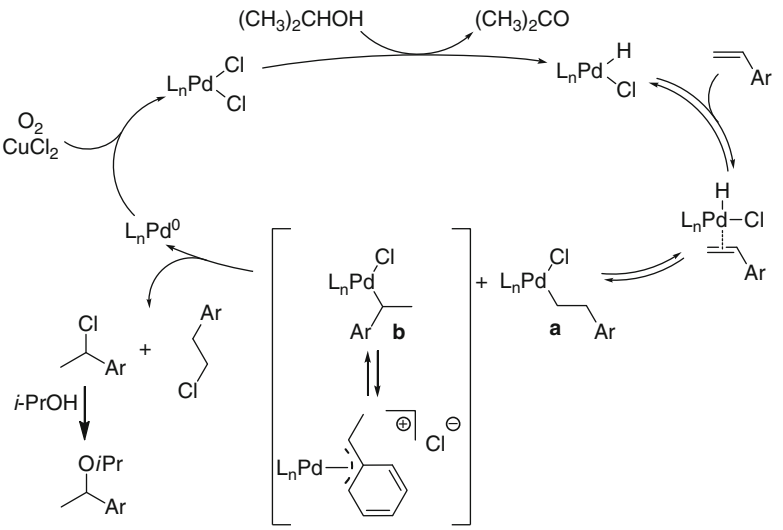
Scheme 47 Styrenes hydroalkoxylation

Sigman reported a particular hydrochlorination/hydroalkoxylation reaction catalyzed by Pd(II) in combination with Cu(II), starting from styrenes. The first formed hydrochlorinated product in the presence of an alcohol was converted in situ to benzylic ethers [96] (Scheme 47).

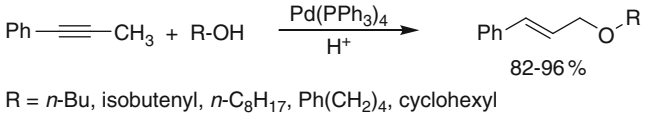
The proposed mechanism initially showed the formation of a Pd hydride intermediate by an alcohol oxidation. The styrene substrate is then coordinated to Pd, followed by insertion of the double bond into the Pd hydride. Both Pd alkyls **a** and **b** are formed; however, **b** can be stabilized through a π-benzyl intermediate, and thus is likely formed predominantly. Reductive elimination or nucleophilic attack by an exogenous chloride ion gave the halogenated product, which only in the case of electron-rich substrates was transformed into the ether product, through a metal-assisted S_N1 reaction (Scheme 48). In the case of more electron-poor aromatic substrates, the rate of this step is slow enough to allow for isolation of the chloride.

6.2.2 Alkynes

Few reports are known for hydroalkoxylation of alkynes compared to hydroamination partly due to the diminished nucleophilicity and the weaker



Scheme 48 Mechanism proposed for styrenes hydroalkoxylation

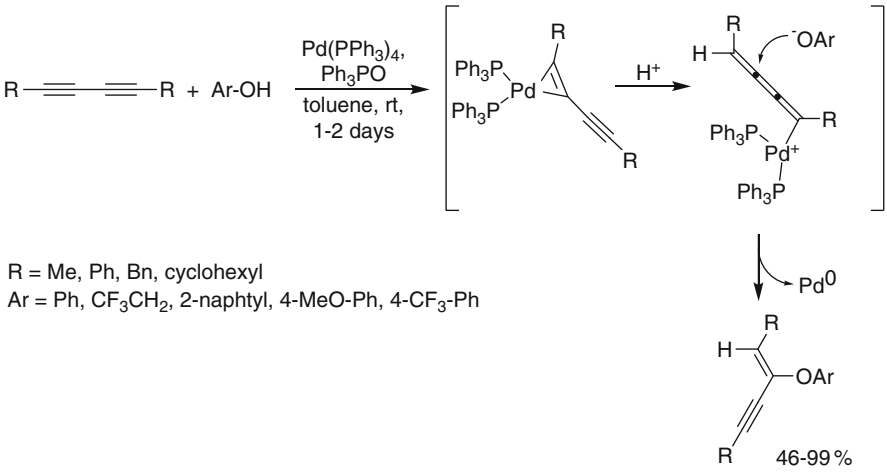


Scheme 49 Alkynes hydroalkoxylation

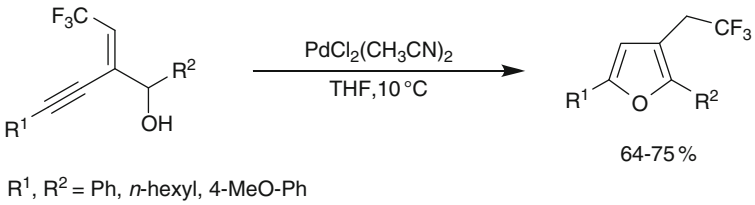
Lewis base character of oxygen nucleophiles. Yamamoto was the pioneer in the addition reactions of alcohols pronucleophiles to alkynes to give allylic ethers [97–99]. In general, the reaction of the internal alkyne with alcohols in the presence of a catalytic amount of $Pd(PPh_3)_4$ and benzoic acid in dioxane at 100°C gave the allylic ethers in good yields (Scheme 49). The presence of AcOH enhanced the yields supporting the formation of the hydridopalladium intermediate species (see mechanism in the introduction). Furthermore, the intramolecular reaction of alkynes having a hydroxyl group at the terminal carbon gave five- and six-membered cyclic ethers in good yields.

In the case of conjugated diynes, the hydroalkoxylation reaction in the presence of phenol afforded alkoxylated enyne products. Aliphatic alcohols do not add to the diyne system indicating the necessity of an acidic alcohol (phenols, naphthol or 2,2,2-trifluoroethanol). The mechanism supposed the formation of a σ-cumulenyl palladium complex intermediate is consistent with the absence of the double addition of phenol to the starting diyne or the second addition of phenol to the resulting enyne [100] (Scheme 50).

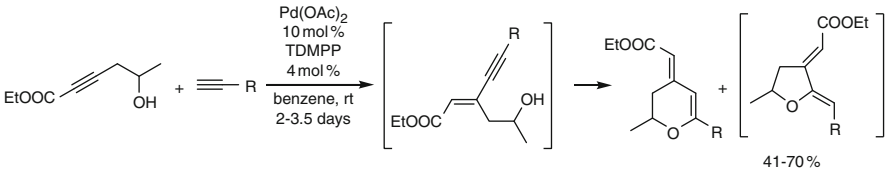
Among the intramolecular processes aimed to the heterocyclic synthesis, a tandem procedure realized through $Pd(PPh_3)_4$ catalysis was applied to the



Scheme 50 Diynes hydroalkoxylation



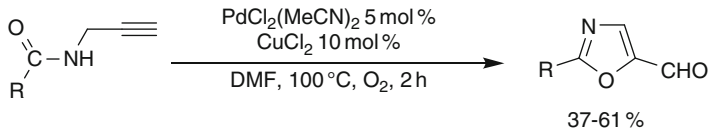
Scheme 51 Intramolecular hydroalkoxylation/isomerization processes



Scheme 52 Tandem addition/cyclization processes

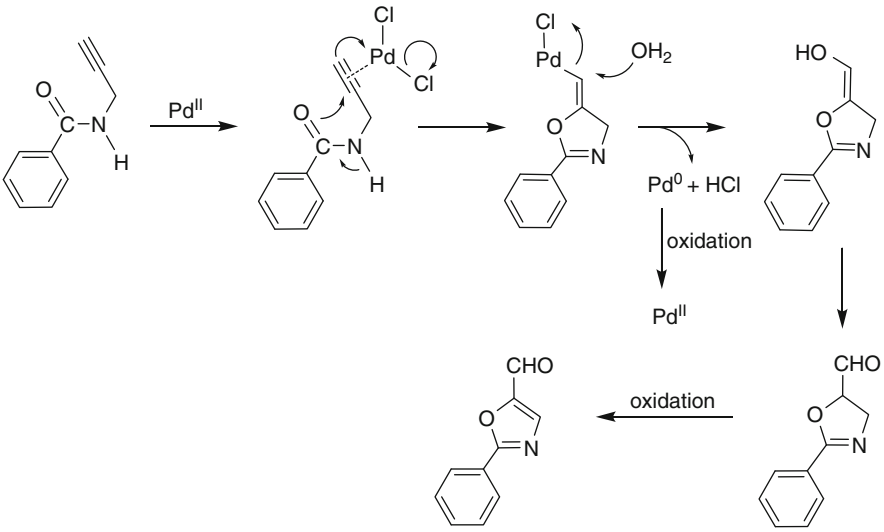
formation of 3-trifluoroethylfurans, consisting on the addition of terminal alkynes to 2-substituted trifluoromethyl allylic alcohols followed by cyclization and subsequent isomerization [101] (Scheme 51).

In a similar economical process, dihydropyrans were obtained in good yields using $Pd(OAc)_2$ and TDMPP (tris(2,6-dimethoxyphenyl)phosphine), through a 6-*endo-dig* cyclization process. The regioisomeric tetrahydrofuran adduct arising from 5-*exo-dig* cyclization was in some cases observed as minor product [102] (Scheme 52).



R = *n*-Bu, 4-MeOPh, 4-NO_2Ph, $BnCH_2$, 2-thienyl, 2-pyrrolyl, 2-furyl, CH(Me)NHBoc

Scheme 53 Intramolecular propargylamides reaction

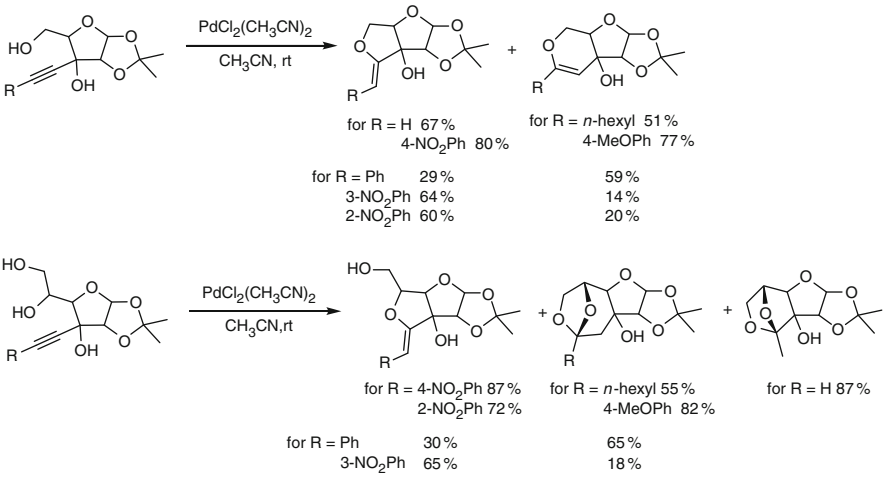


Scheme 54 Mechanism for 5-formyl-oxazoles formation

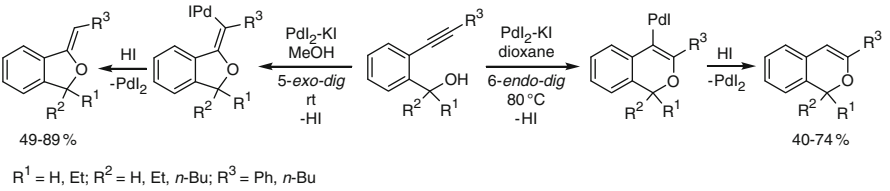
The construction of 2-substituted 5-formyl-oxazoles was performed starting from aryl, heteroaryl, and alkyl propargylamides through treatment with Pd(II) salts with tolerance of various functional groups [103] (Scheme 53).

The proposed mechanism hypothesized the nucleophilic attack of the oxygen to the Pd-complexed C–C triple bond, through the enol amide form, producing the oxazole skeleton by formation of the σ-alkenylpalladium complex. The intervention of water provided, through its enol form, the 4,5-dihydrooxazole-5-carbaldehyde. The oxidizing system also promoted the dehydrogenation step (Scheme 54).

Recent studies related to Pd-catalyzed competitive *exo*- vs *endo*-cyclizations of alkynols were reported by Ramana group [104, 105]. Cycloisomerization of 3-C-alkynyl-allo- and ribofuranose derivatives was investigated in detail to understand the influence of electronic factors on the regioselectivity in ring closure reaction. The reactions in general are influenced by the electronic nature of the substituent on the alkyne unit. A preference for *endo-dig* cyclization over *exo-dig* is noted, if the alkynyl substituent is not sufficiently electron withdrawing. In the



Scheme 55 Regioselectivity in cyclization of sugar alkynols



Scheme 56 Regioselectivity in cyclization of 2-alkynylbenzyl alcohols

homologous 3-C-propargyl furanose derivatives, the competitive *6-exo-dig* vs *7-endo-dig* cyclization leading to a six- or seven-membered ring was investigated (Scheme 55).

The cyclization of 2-alkynylbenzyl alcohols promoted by the catalytic system PdI_2-KI, led to the formation of 1,3-dihydroisobenzofurans and/or isochromenes. The preference toward the 5-*exo-dig* cyclization or the 6-*endo-dig* cyclization was dependent on the substitution pattern of the substrate as well as reaction conditions. On the basis of experimental results, some generalizations can be highlighted to favor 5-*exo-dig*-cyclization: (a) aryl rather than alkyl substitution on the triple bond; b) α dialkyl substitution to the hydroxyl group; (c) higher solvent polarity; (d) lower reaction temperature [49] (Scheme 56).

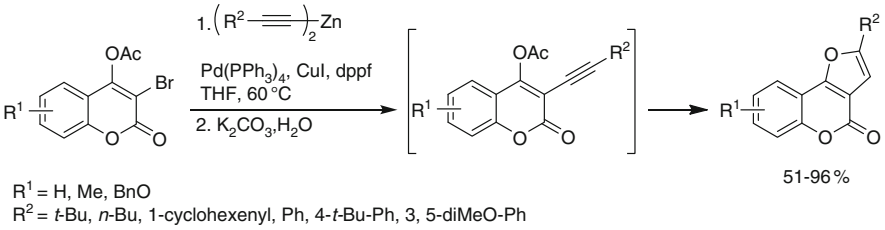
1,3-Dihydroisobenzofurans are obtained also in a one-pot procedure, without the isolation of 2-alkynyl benzyl alcohols, in a domino process that comprises a Sonogashira coupling followed by an intramolecular hydroalkoxylation, starting from 2-halobenzyl alcohols and phenylacetylene, using only NHC-Pd-pyridine complexes prepared to this aim [106]. The choice of the catalyst was fundamental, very low reactivity in the hydroalkoxylation step was observed performing the

reaction with $Pd(OAc)_2$ or $PdCl_2(PPh_3)_2$. The study tried to find a useful balance of the electronic properties of the ligands to afford a catalyst that is active in both reactions at the same time.

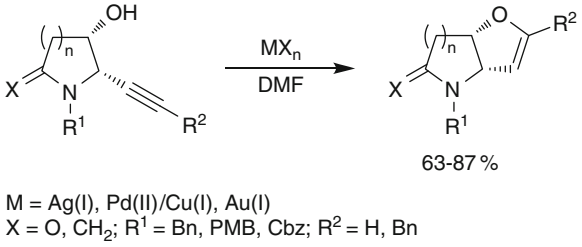
A one-pot sequential Pd/Cu catalyzed alkynylation followed by intramolecular hydroalkoxylation was reported to achieve furo[3,2-*c*]chromen-4-ones starting from easily available 3-bromo-4-acetoxycoumarins and 1-alkynes [107]. The key step involved alkynylation with in situ prepared dialkynylzinc reagents followed by intramolecular hydroalkoxylation, without isolation of the 3-alkynyl-4-acetoxy coumarin intermediate (Scheme 57).

Bicyclic furo[3,2-b]pyrrole and furo[3,2-b]pyridine systems were prepared through a cycloisomerization reaction of *cis*-4-hydroxy-5-alkynylpyrrolidinones and *cis*-5-hydroxy-6-alkynylpiperidinones using Pd(II)-complex [108] (Scheme 58).

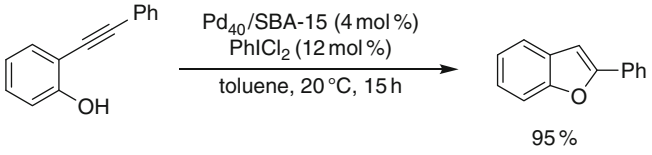
A highly active heterogeneous palladium nanoparticle catalyst for the hydroalkoxylation of 2-phenylethynylphenol was developed and employed in a continuous flow reaction system. The best of the catalyst efficiency was observed when employed in conjunction with $PhICl_2$ [109] (Scheme 59).



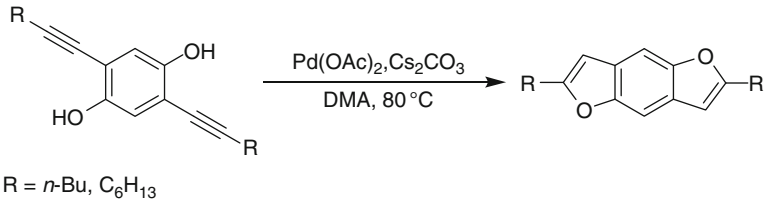
Scheme 57 Sequential process to furo[3,2-c]chromen-4-ones



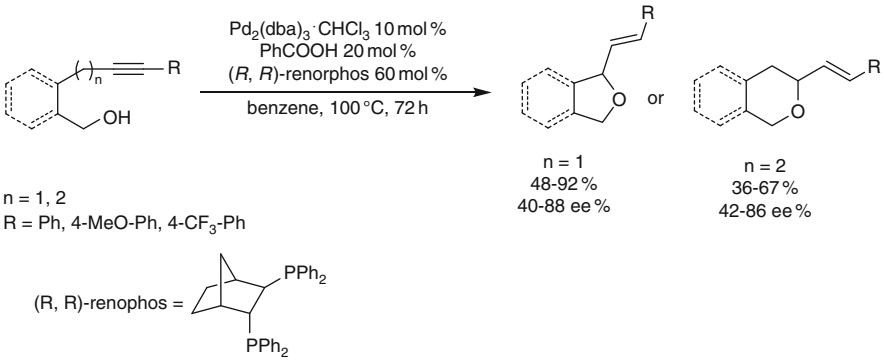
Scheme 58 Intramolecular hydroalkoxylation to achieve bicyclic systems



Scheme 59 Hydroalkoxylation of 2-phenylethynylphenol



Scheme 60 Double hydroalkoxylation of dihydroxy dialkynylbenzenes



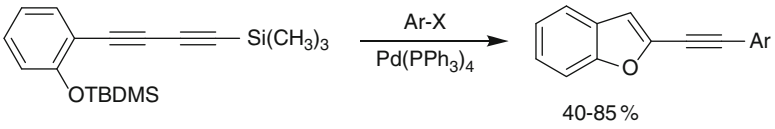
Scheme 61 Chiral catalyst for enantioselective cyclic ethers formation

Double cycloisomerization of dihydroxy-substituted dialkynylbenzenes utilizing $Pd(OAc)_2$ and Cs_2CO_3 was a convenient synthetic route to construct disubstituted benzodifurans [110] (Scheme 60).

In the presence of the chiral palladium catalyst generated from $Pd_2(dba)_3{\cdot}CHCl_3$ and (*R*, *R*)-renorphos, alkynols undergo catalytic asymmetric intramolecular hydroalkoxylation in a manner similar to hydroamination, allowing the enantioselective synthesis of cyclic ethers (Scheme 61). The reaction represents the first example of transition-metal catalyzed asymmetric intramolecular addition of oxygen to an activated C–C bond, even if some limitations, such as high catalyst loading, high temperature, and longer reaction times were reported. This reaction was very sensitive to the electronic effect of substituents at the aromatic ring attached at the terminus of the alkynes (electron-donating substituents on the aromatic group gave lower yields and ee's) [111].

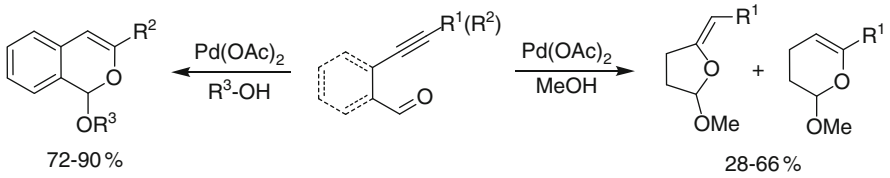
Among the known methodologies for the synthesis of benzofuran derivatives, a favorable recent alternative to obtain 2-alkynylbenzofurans was represented by the intramolecular reaction of the *ortho* diyne phenols and aryl halides. This procedure may be performed with success in one or two steps in the presence of $Pd(PPh_3)_4$ [112] (Scheme 62).

A particular pathway for the synthesis of cyclic alkenyl ethers by intramolecular C–O bond formation consisted in the reaction of γ-acetylenic aldehydes in the



Ar = Ph, 4-Me-Ph, 4-NH_2-Ph, 4-NO_2-Ph, 4-MeO-Ph, 3-Py, 2-thiophenyl

Scheme 62 Synthesis of 2-alkynylbenzofurans



R^1 = Ph, 4-Me-Ph, 4-CF_3-Ph, C_8H_{17}; R^2=*n*-Bu, Ph, $SiMe_3$; R^3 = Me, Et, *i*-Pr

Scheme 63 Intramolecular cyclization of γ-acetylenic aldehydes

presence of MeOH and Pd(II), the latter exploiting the double role of Lewis acid and transition metal (Scheme 63).

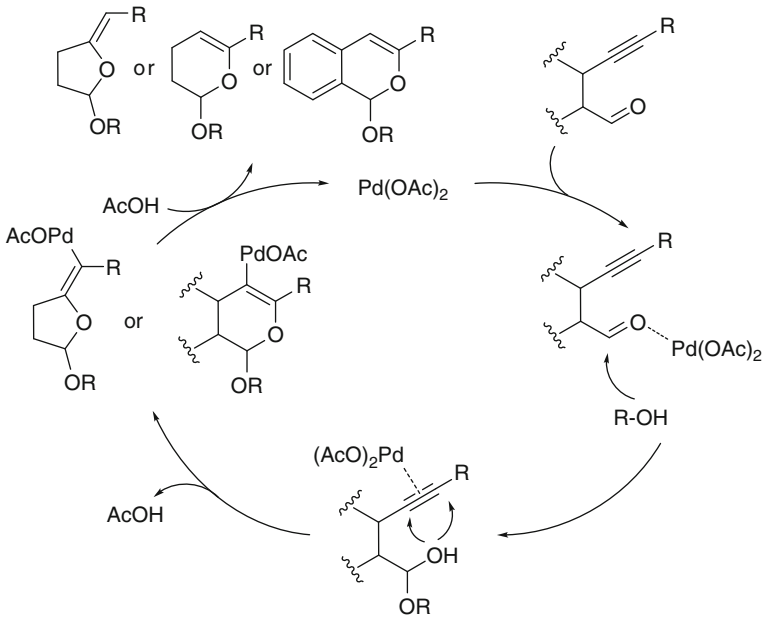
The Lewis acid forms a complex with the carbonyl oxygen and makes feasible the attack of MeOH to produce an hemiacetal. The coordination of the triple bond to Pd(II) would induce the intramolecular attack of the hydroxyl moiety to the alkyne from the opposite side to the palladium via the *exo* or *endo* pathway to produce the corresponding vinylpalladium complex. The protonation of these intermediates gives the alkenyl cyclic ethers. The cyclization was effective with $Pd(OAc)_2$ and BQ, which did not work as an oxidizing agent but as a ligand for the palladium catalyst [113] (Scheme 64).

A challenging microwave assisted three-component approach to dihydroisobenzofurans and dihydrofuro[3,4-*b*]pyridines starting from *o*-bromoarylaldehydes, methanol and terminal alkynes was recently published by our group [114]. The reaction occurs through an interesting cooperative palladium/base promoted coupling/addition/cyclization sequence (Scheme 65).

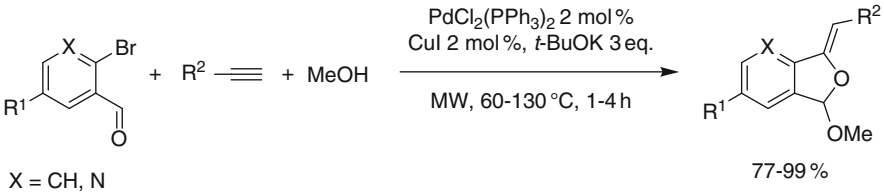
6.3 Hydroacyloxylation

6.3.1 Alkenes

The acetyloxylation of alkenes bearing electron-withdrawing substituents afforded the corresponding acetic esters, using $PdCl_2(CH_3CN)_2$ as catalyst in the presence of LiCl [115]. Similarly, the addition of carboxylic acids across dienes with $Pd(PPh_3)_4$ gave allyl esters in good yields [93] (Scheme 66).



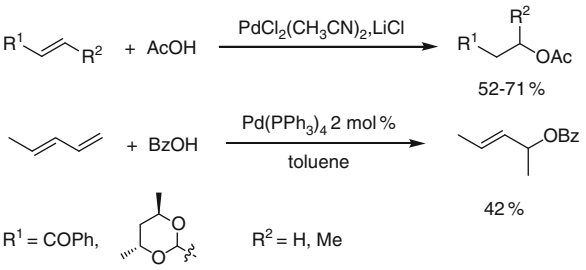
Scheme 64 Mechanism of γ-acetylenic aldehydes cyclization



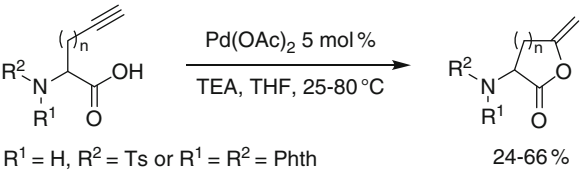
Scheme 65 Three-component approach to dihydroisobenzofurans synthesis.

6.3.2 Alkynes

Among different variety of existing method for preparing functionalized heterocycles, the intramolecular cyclization of unsaturated systems bearing a carboxylic acid provided lactones of different size. Enantiomerically pure α-amino acids containing a carbon–carbon triple bond were exploited as starting materials for the synthesis of various heterocycles through a Pd-catalyzed intramolecular cyclization, involving the carboxylate or amine functionality, depending on the protecting group strategy applied. Thus, the cyclization of esterified aminoacids produced nitrogenated heterocycles; conversely, the *N*-protected amino acids furnished the corresponding five- and six-membered α-amino-γ-methylidene



Scheme 66 Acetoxylation of alkenes and dienes



Scheme 67 Intramolecular hydroacyloxylation of alkynes

lactones [116, 117] (Scheme 67). In contrast with the five-membered rings, the six-membered lactones were obtained in somewhat disappointing yields, which is probably due to the lower tendency of Pd to react in a 6-*exo*-fashion. The ^{1}H NMR experiments led to conclude that virtually no racemization occurred in these cyclization reactions.

7 Platinum

7.1 Hydration

7.1.1 Alkenes

Platinum(II) complexes have been described as catalysts for the hydration of both terminal alkenes in an anti-Markovnikov fashion and for symmetric maleic acid derivatives.

Unfortunately, the reported [118] direct anti-Markovnikov hydration of terminal alkenes catalyzed by *trans*-PtHCl(PMe_3)$_2$ in the presence of aqueous NaOH and a phase-transfer catalyst at 60–100°C has proved to be irreproducible [119, 120].

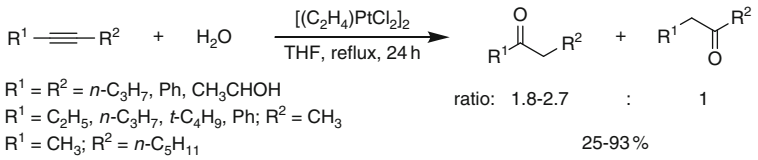
Bennett and coworkers described the *cis*-hydroxyplatination of diethyl maleate with organoplatinum(II)-hydroxo complexes [121]. In particular, they isolated and characterized the *cis*-PtMe{CH(CO_2Me)CH(OH)(CO_2Me)}L_2 [L_2 = 2 PPh_3 or dppe] complexes. Treatment of these complexes with aqueous acid cleaves the

Pt-CH(CO_2Me)CH(OH)(CO_2Me) bonds forming [PtMe(H_2O)L_2]$^+$ and dimethyl malate, $MeO_2CCH_2CH(OH)CO_2Me$, and demonstrated that two steps are necessary for the catalytic addition of water to dimethyl maleate. More recently, the synthesis and solution- and solid-state characterization of monometallic Pt(II) complexes of the biphosphine ligands bearing two *o-N,N*-dimethylanilynyl substituents at each P-atom were described [122]. Some of these complexes show marginal activity in water for the catalyzed hydration of maleic to malic acid, giving about 6–7% conversion in 24 h at 100°C at a catalyst loading of 100:1.

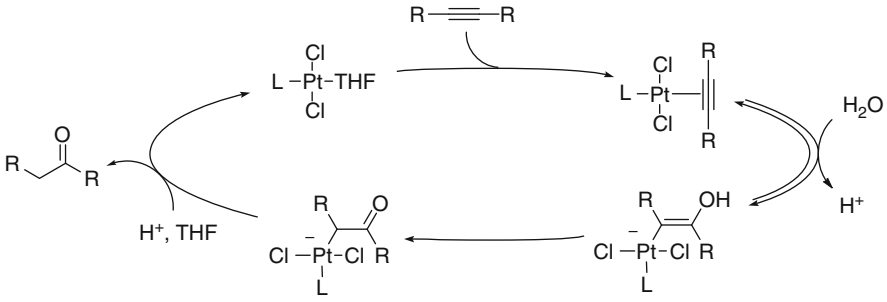
7.1.2 Alkynes

The platinum-catalyzed hydration reactions of alkynes have been recently reviewed [1a, e]. The early works in this field refer to the use of simple platinum(II) halides or of Zeise's Pt(II) dimer, [{$PtCl_2(C_2H_4)_2$}$_2$], as active and selective catalysts for the hydration of unactivated terminal and internal alkynes [123–125] (Scheme 68). Unfortunately, for unsymmetrically substituted alkynes, the reported regioselectivities are poor.

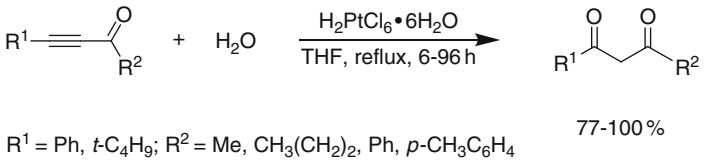
The accepted reaction mechanism involves coordination/activation of the triple bond to the metal followed by water addition, enol-ketone tautomerization followed by protonolysis (Scheme 69).



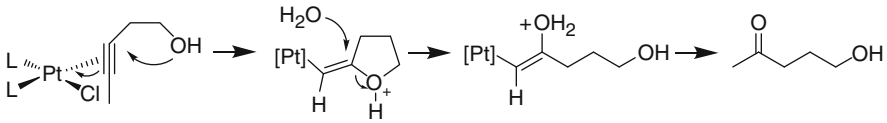
Scheme 68 Pt(II) catalyzed hydration of alkynes



Scheme 69 Reaction mechanism for Pt(II) catalyzed hydration of alkynes



Scheme 70 Pt(IV) catalyzed hydration of alkynones



Scheme 71 Pt(II) catalyzed hydration of 3-pentyn-1-ol

Besides, the works of Blum and coworkers established that the hydration of alkynones to the corresponding 1,3-diketones could be easily accomplished in the presence of the platinum (IV) compound $H_2PtCl_2 \cdot 6\ H_2O$ [126] (Scheme 70).

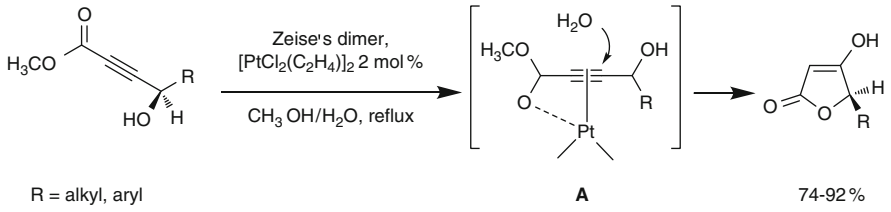
Moreover, both aliphatic and aromatic unactivated alkynes can be hydrated with a catalyst generated from $PtCl_4$ and CO at 40–110°C. This powerful catalyst is able to operate under homogeneous conditions in wet THF or, under phase-transfer conditions, in $CHCl_3/H_2O$ in the presence of a quaternary ammonium salts [127, 128]. The active species is a Pt(II) compound [PtH(CO)Cl(L)] (L = CO, H_2O, THF) and the reaction mechanism parallels that reported for platinum(II) halides and Zeise's catalyst. The reactions work with internal and terminal alkynes, following in the latter case the Markovnikov rule. Scarce reproducibility and erratic yields are the main drawbacks in these reactions.

The catalytic hydration of alkynes in water was developed with water soluble *cis*-$(TPPTS)_2PtCl_2$ and $(DPPETS)PtCl_2$ complexes [TPPTS = tris(sodium *m*-benzenesulfonate)phosphine, DPPETS = $(\{m\text{-}NaO_3SC_6H_4\}_2PCH_2CH_2P\{m\text{-}C_6H_4SO_3Na\}_2)$] [129, 130]. These complexes catalyze the hydration of water soluble 3-pentyn-1-ol and 4-pentyn-1-ol to 5-hydroxy-2-pentanone through a mechanism involving a 5-*endo-dig* and 5-*exo-dig* cyclization step, respectively, as shown in Scheme 71 for 3-pentyn-1-ol.

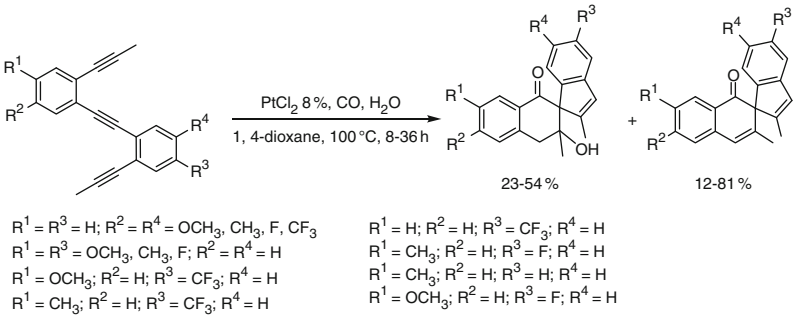
In a heteroannulation reaction, optically active γ-hydroxy-α,β -acetylenic esters undergo regiospecific hydration in the presence of Zeise's dimer, $[PtCl_2(C_2H_4)]_2$, to generate, by tandem hydration/annulation reaction, optically active tetronic acids in 74–92% yields [131] (Scheme 72).

The intermediate **A** has been proposed for the Pt(II)-catalyzed hydration of the γ-hydroxy-α,β-acetylenic esters. In **A**, the electron-withdrawing effect of the ester group, the Lewis acidity of the Pt(II) center, and the chelating effect in the coordination of the acetyleneic ester to the Pt(II) center contributed to the observed regiospecific hydration.

The most recent findings on these reactions were reported by Liu and coworkers who developed a series of cascade reactions involving one or more alkyne



Scheme 72 Zeise's dimer catalyzed hydration/annulation of γ-hydroxy-α,β -acetylenic esters



Scheme 73 $PtCl_2$/CO catalyzed regioselective hydration/cyclization of triynes

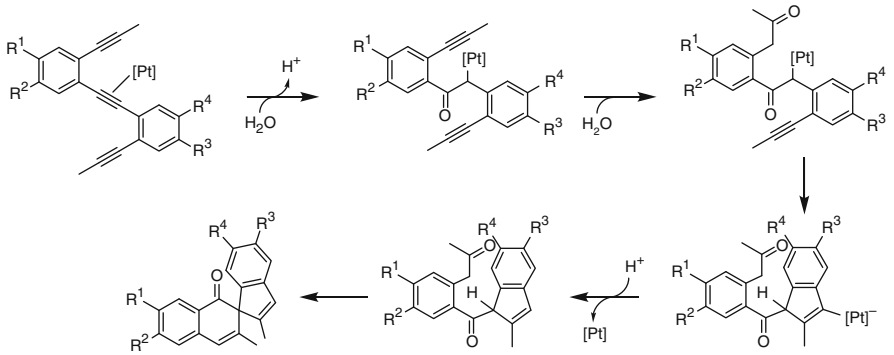
hydration step. The catalyst employed was $PtCl_2$/CO in wet dioxane and the substrates involved trialkynes, oxoalkynes, and oxodiynes for the synthesis of bicyclic spiroketones [132], tetracyclic ketones [133], chrysene derivatives [134], and benzopyrones [135].

Indeed, β-unsaturated bicyclic spiroketones were obtained from triynes via a regioselective cyclization (Scheme 73). Model reactions suggest that the platinum catalyzed reactions include two regioselective hydrations, an alkyne insertion, and an aldol condensation (Scheme 74).

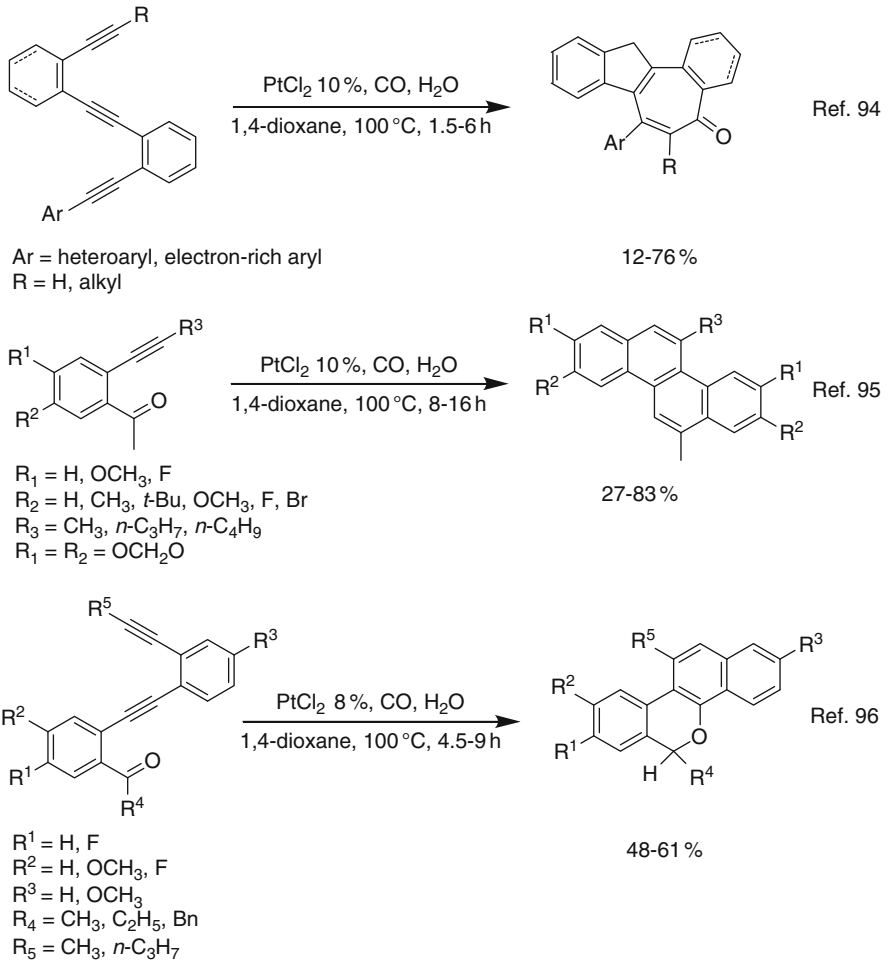
Similar strategies involving hydration/cyclization steps were employed for the synthesis of the other reported polycyclic compounds (Scheme 75).

7.1.3 Nitriles

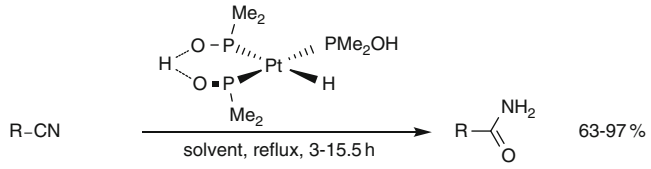
Homogeneous catalysts based on Pt(II) complexes have also been successful in the hydrolysis of nitriles to amides. The early report on this topic appeared about 30 years ago [136, 137]. However, the first reactive and selective catalyst, reported in 1986 by Togler and Jensen [138], was $[PtH(PMe_3)_2(H_2O)][OH]$, a species that catalyzes the hydrolysis of acetonitrile to acetamide at rates of 178 mol/(mol of catalyst h), at 80°C and gives as many as 6000 turnovers.



Scheme 74 Proposed mechanism for $PtCl_2$/CO catalyzed hydration/cyclization of triynes



Scheme 75 $PtCl_2$/CO catalyzed domino hydration/cyclization reactions of triynes, oxoalkynes and oxodiynes



R = CH_3, CH_2 = CH, $CNCH_2CH_2$, Ph, 4-OHC_6H_4, 1,4-CN-C_6H_3, 2,6-F-C_6H_3, 3-CN-pyridine
solvent = H_2O, H_2O/THF, H_2O/EtOH

Scheme 76 Platinum phosphinito catalyzed hydrolysis of nitriles

With acrylonitrile, the same catalyst exhibits low regioselectivity between the olefin and nitrile functionalities at 80°C, whereas at 25°C, regioselectively (97%) hydrates 6.1 mol of acrylonitrile/(mol of catalyst h) to acrylamide.

However, the most recent and useful applications of Pt catalysis to the hydrolysis of nitriles to amide were achieved with homogeneous platinum phosphinito catalysts [139, 140]. The catalyst precursors are coordination compounds of Pt(II) with secondary phosphine oxides and the results obtained with [PtH(PMe_2OH)(PMe_2-O)$_2$H] with alkyl, alkenyl, and aryl nitriles are reported in Scheme 76.

The catalyst contains a hydrogen bridged mono-anionic bidentate phosphinito group, together with a third phosphine oxide ligand and a monodentate anionic ligand, a hydride ion. The reaction of the hydride with water gives a cationic species, which is the active catalyst. The suggested reaction mechanism is reported in Scheme 77.

On coordination to the cation, the nitrile becomes susceptible to nucleophilic attack. The hydrolysis gives the amide as the sole product, and there is no tendency toward further hydrolysis to the acid. It is noteworthy to report that hydration of acrylonitrile to acrylamide was achieved with a turnover number of 77,000, without addition to the C=C double bond.

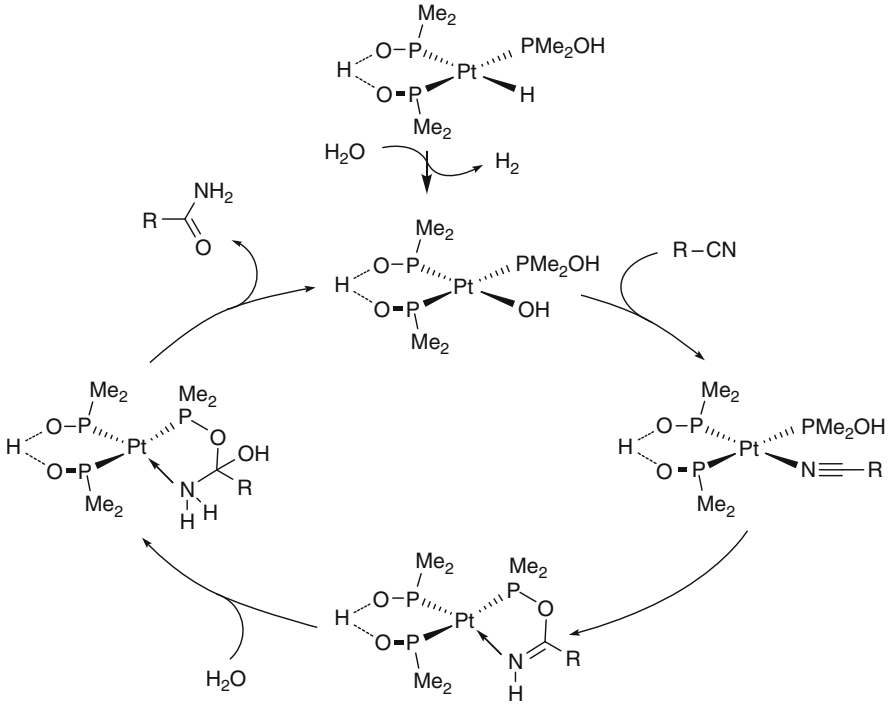
More recently, broadening the scope of these hydration reactions, hydrolysis of several hindered or acid-, base-sensitive nitriles, with the same catalyst, has been achieved with moderate and more often excellent yields (25–98%) [141] (Fig. 3).

The same authors reported that a new catalyst precursor bearing optical active phosphine ligand failed to give kinetic resolution and racemize during the reaction.

7.2 Hydroalkoxylation

7.2.1 Alkenes

Platinum-mediated additions of alcohols to alkenes are known in their intramolecular version and have been developed by R. A. Widenhoefer and coworkers [142]. Thus, they showed that [{$PtCl_2(H_2C\text{-}CH_2)$}$_2$]/2P(4-$C_6H_4CF_3$)$_3$ is an effective catalyst for the intramolecular cyclization of γ- and δ-hydroxyolefins to saturated oxygen heterocycles under mild reaction conditions [143] (Scheme 78).



Scheme 77 Suggested mechanism for Pt phosphinito catalyzed hydrolysis of nitriles

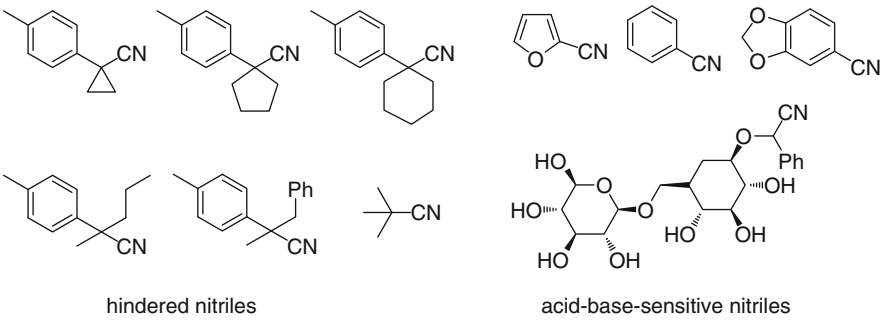
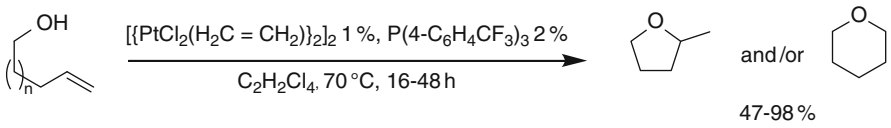
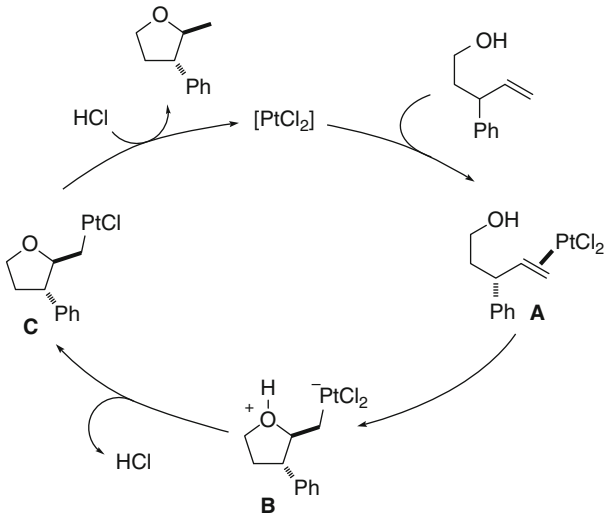


Fig. 3 Hindered and acid- base-sensitive substrates for Pt-catalyzed hydration

The reactions tolerate a wide range of functional groups and give rise to the product arising from oxygen addition to the more substituted alkene carbon atom. The platinum-catalyzed hydroalkoxylation mechanism involves outer-sphere attack of the pendant hydroxyl group on the platinum-complexed alkene (**A**) to form zwitterion **B**. Loss of HCl followed by protonolysis of the Pt–C bond of **C** would release the oxygen heterocycle with regeneration of the Pt(II) catalyst (Scheme 79).



Scheme 78 Pt(II) catalyzed cyclization of γ- and δ-hydroxyolefins

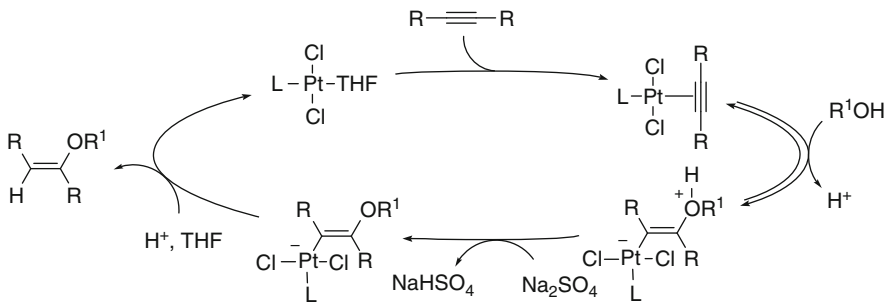


Scheme 79 Proposed mechanism for Pt(II) catalyzed cyclization of γ- and δ-hydroxyolefins

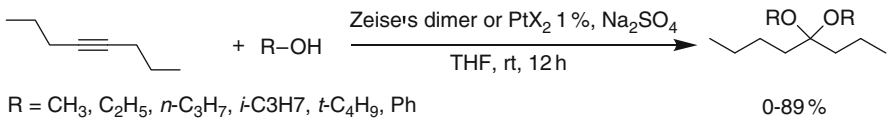
7.2.2 Alkynes

A study on the intermolecular addition of alcohols to alkynes in the presence of Pt (II) (as Zeise's dimer or as simple dihalide salt) has been reported by Hartman in 2004 [144]. The proposed reaction mechanism parallels the hydration mechanism shown in Scheme 65. However, the nucleophilic addition, shown in step 2, is reversible when tautomerism to a carbonyl is not available, which would be the case if alcohol was the nucleophile. Thus, if alcohol is used as the nucleophile, the initial product would be a platinum-bound protonated vinyl ether in the equilibrium shown in Scheme 80. Since tautomerism is not possible for this species, then the addition of an appropriate base could abstract the acidic proton from the intermediate and drive the equilibrium forward.

Scheme 81 summarizes the results obtained using anhydrous sodium sulfate with platinum(II) in adding a series of alcohols to 4-octyne. The results clearly indicate that the cocatalyst provides high conversions of the alkyne to the corresponding acetal products. In the absence of the cocatalyst, only starting alkyne and alcohol are isolated.



Scheme 80 Proposed mechanism for Pt(II) catalyzed intermolecular addition of alcohols to alkynes



Scheme 81 Pt(II) catalyzed hydroalkoxylation of 4-octyne

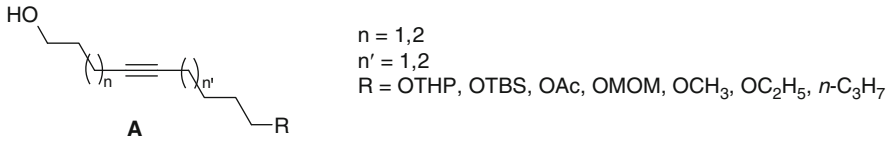
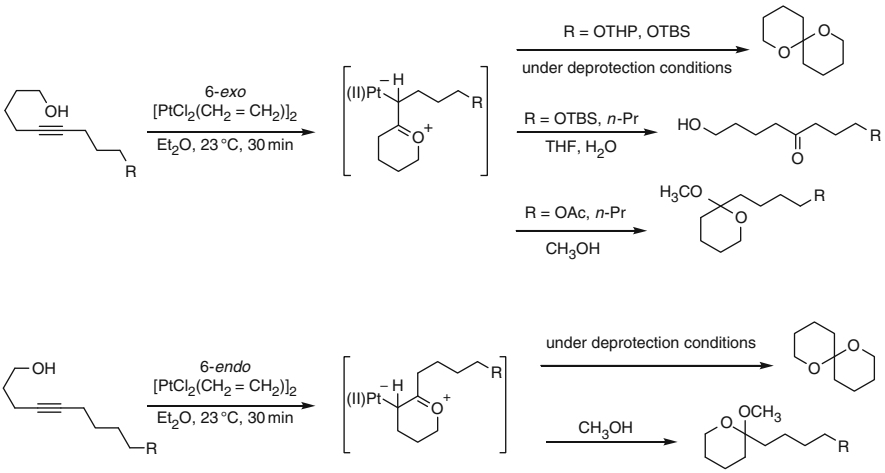


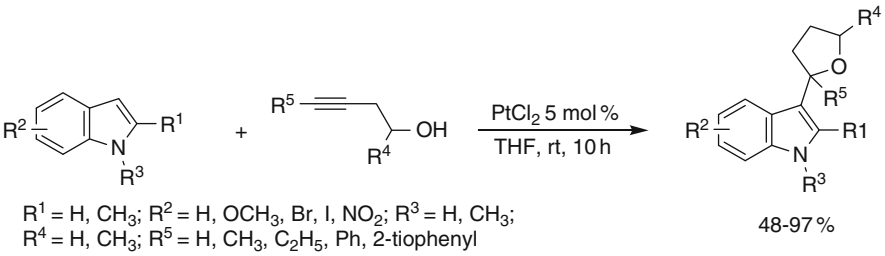
Fig. 4 Internal alkynes precursors for the synthesis of spiroketals, acetals and ketones

Attempts to limit the addition of alcohol in order to observe and isolate a vinyl ether failed resulting in the isolation of the alkyne and variable amounts of the acetal. This seems to suggest that the second alcohol addition to the platinum-bound vinyl ether is faster than the primary addition of alcohol to the alkyne. This peculiar behavior has been successfully applied into the oxy-functionalization of internal alkynes bearing one or two oxy-substituents, general formula **A**, Fig. 4, for the synthesis of spiroketals, acetals, and ketones [145].

5-Alkynols (Fig. 4, n = 2, n' = 1, R = OTHP, OTBS, OAc, n-Pr) undergo selective intramolecular 6-*exo* vs 7-*endo* hydroalkoxylation in the presence of Pt (II) Zeise's dimer giving rise to transient platinated oxocarbenium species, Scheme 82. In a second step, the derivatization of the platinated intermediate affords the final products. When R is a THP- or TBS-protected oxygen, the reaction, upon deprotection conditions, involves a second cyclization to spiroacetal derivatives. The OTBS and n-Pr derivatives in the presence of moist THF yield the corresponding δ-hydroxyketones, whereas, with methanol, OAc and n-Pr derivatives afford the corresponding methylacetals.



Scheme 82 Zeise's dimer catalyzed intramolecular hydroalkoxylation of 4- and 5-alkynols



Scheme 83 $PtCl_2$ catalyzed tandem nucleophilic addition/intramolecular hydroalkoxylation of 3-pentynols with indoles

The Pt(II) catalyzed hydroalkoxylation of 4-alkynols (Fig. 4, n = 1, n' = 2, R = OTHP, OTBS, OAc, Et, OMOM, OMe) followed by derivatization as before favors the 6-*endo* derived products with a 5-*exo*:6-*endo* selectivity ranging from 1:1.7 to 1:11, depending on R and derivatization method. For 4-alkynols, 5-*exo* selectivity has been achieved with a combination of $MeAuPPh_3/AgPF_6$.

With these results in hand, the same authors described a tandem hydroalkoxylation/acetal formation upon the reaction of 5-alkynols with five equivalents of MeOH in the presence of 1% of Pt(II) Ziese's dimer in a THF:$HC(OMe)_3$ (10:1) solvent mixture.

In a tandem intramolecular version of these reactions, starting from 3-pentynols under Pt(II) catalysis, initially formed enol ethers undergo Pt(II) catalyzed nucleophilic attack, the nucleophile being the C-3 of an indole derivative [146]. The reaction works in THF, at room temperature and in the presence of $PtCl_2$ with a wide range of substituted 3-alkynols and indoles (Scheme 83).

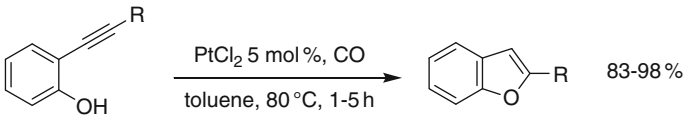
Simple intramolecular 5-*endo-dig* hydroalkoxylation of phenol derivatives, bearing an alkyne moiety at the ortho-position, gives rise to the corresponding

benzofurans on exposure to catalytic amounts of $PtCl_2$ in toluene [147]. The reaction proceeds at ambient temperature, although it is significantly faster when performed at 80°C. Low catalyst loadings (0.5–1 mol %) usually suffice to obtain almost quantitative yields with a wide range of substrates also under air at room temperature (Scheme 84). In contrast to most other catalysts used for similar purposes, no external base is necessary to promote the reaction, which is also compatible with functional groups that are susceptible to oxidative insertion of low-valent metal species. A mechanistic rationale is proposed, implying activation of the alkyne by the carbophilic Pt(II) as the primary step of the catalytic cycle.

In the same paper, the authors extended the procedure to O-substituted phenols (phenolic ethers such as allyl, methoxymethyl (MOM), benzyloxymethyl (BOM), and (trimethylsilyl)ethoxymethyl (SEM)) and the substituent is transferred from oxygen to carbon-3, thus allowing for an intramolecular carboalkoxylation. Although some of these reactions can even be carried out in air, the rates are significantly increased when conducted under an atmosphere of CO.

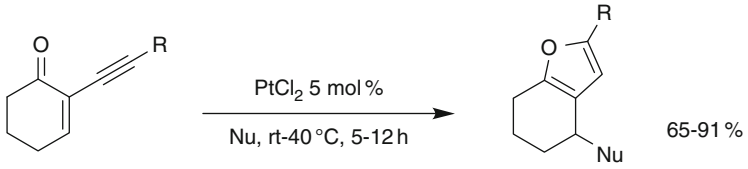
1,4-Nucleophilic addition to enynones and 1,2-nucleophylic addition to γ-ketoalkynes generate in situ the suitable functionalities for subsequent intramolecular hydroalkoxylations under Pt(II) catalysis.

Thus, tandem nucleophiles addition to cyclic and acyclic enynones followed by intramolecular hydroalkoxylation reaction allows for the synthesis of highly substituted or fused bicyclic furan derivatives [148] (Scheme 85).



R = *n*-C_3H_7, *n*-C_5H_{11}, *cyc*-C_3H_5, $(CH_2)_2Ph$, $CH_2CH(COOCH_3)_2$, Ph, *p*-$CH_3OC_6H_4$, *m*-$CF_3C_6H_4$

Scheme 84 $PtCl_2$ catalyzed intramolecular hydroalkoxylation of o-alkynylphenols



R = H, *n*-C_3H_7, *t*-Bu, cyclohexenyl, Ph, TMS, $NC(CH_2)_3$
Nu = H_2O, CH_3OH, *n*-C_4H_9OH, *i*-C_3H_7, allyl alcohol, propargyl alcohol, Ph, $C_6H_5NH_2$, CH_3COOH, $PhCH_2COCH_2Ph$

Scheme 85 $PtCl_2$ catalyzed tandem nucleophiles addition/intramolecular hydroalkoxylation of enynones with nucleophiles

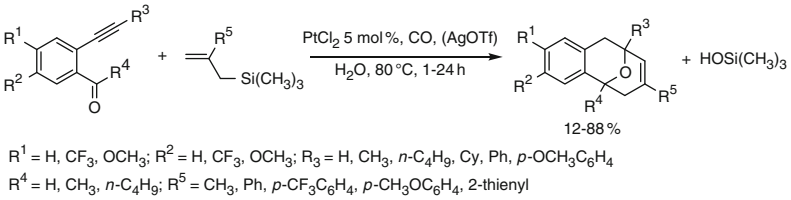
The reactions are performed in the presence of 5 mol% of $PtCl_2$ at temperatures ranging from rt to 60°C and resulted in the simultaneous formation of a new C–O bond and a C–O, C–N or C–C bond depending on the nucleophile.

In a conceptually similar approach, 2-alkynyl-1-carbonylbenzenes and allylsilanes undergo an allylation/annulation cascade reaction in water and in the presence of 5 mol% of $PtCl_2$/CO giving rise to 9-oxabicyclo[3.3.1]nona-2,6-dienes [149] (Scheme 86). This reaction sequence is proposed to proceed through a series of three reactions, including allylation of the carbonyl group, hydroalkoxylation of the alkyne, and a new ene-oxonium annulation.

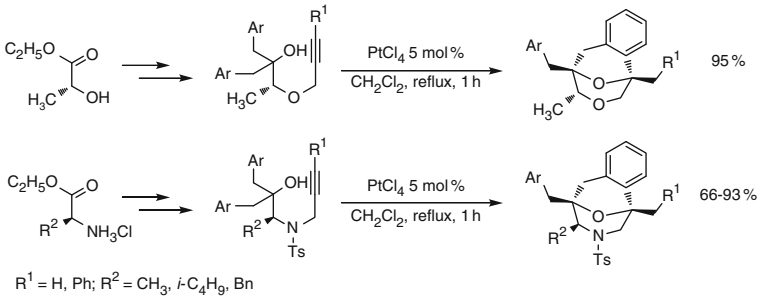
Recently, Barluenga and Fañanás reported tandem intramolecular hydroalkoxylation/hydroarylation and hydroalkoxylation/Prins-Type annulation reactions. In the first communication, they described the cycloisomerization of 5-alkynols with several gold, platinum, and silver catalysts and the application to the synthesis of enantiopure benzo fused cyclic ethers from the chiral pool [150] (Scheme 87).

All reported experiments allow to determine that both cationic Pt(II) and Au(I) and also Pt(IV) complexes were appropriate catalysts for the synthesis of simple and enantiopure bicyclo[3.3.1]nonanes. A mechanism based on a tandem sequence involving a 6-*exo*-cycloisomerization reaction followed by an intramolecular hydroarylation process has been proposed (Scheme 88).

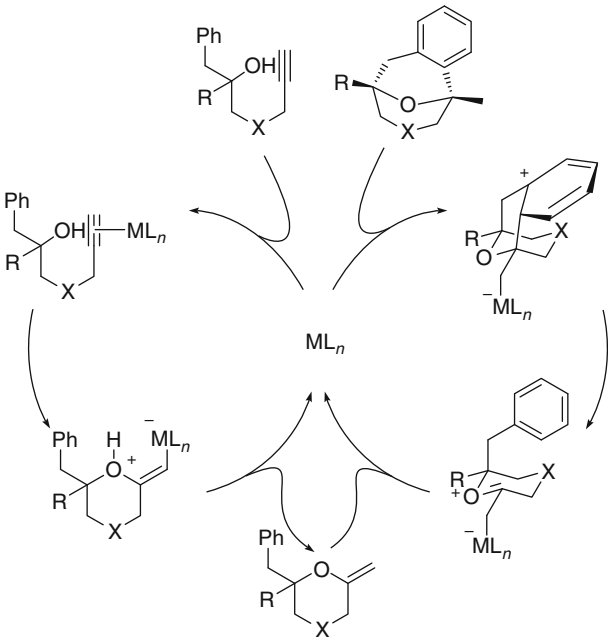
This reaction has been extended to the synthesis of 2,3-benzofused 8-oxabicyclo [2.3.1]octane and thus applied in the key step of the synthesis of Bruguierol A [151].



Scheme 86 $PtCl_2$/CO catalyzed allylation/annulation cascade reaction of 2-alkynyl-1-carbonylbenzenes and allylsilanes



Scheme 87 $PtCl_4$ catalyzed cycloisomerization of 5-alkynols



Scheme 88 Proposed mechanism for cycloisomerization of 5-alkynols

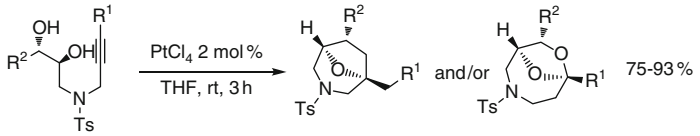
80-96 %

R^1 = H, allyl, CH_3, *n*-C_4H_9, *i*-C_3H_7, *t*-C_4H_9 R^2 = CH_3, *i*-C_3H_7, *i*-C_4H_9, $CH_3S(CH_2)_2$;
R^3 = H, CH_3, C_2H_5, C_3H_7, Ph; X = O, NTs

Scheme 89 $PtCl_4$ catalyzed intramolecular hydroalkoxylation/Prins-type cyclization of 5-alkynols

Moreover, in a subsequent paper, a reaction based on a gold- or platinum-catalyzed tandem process that involves an intramolecular hydroalkoxylation of a triple bond followed by a Prins-type cyclization has been reported for the synthesis of [3.3.1]bicyclic compounds starting from easily available alkynol derivatives [152] (Scheme 89).

The reaction has been carried out with differently substituted alkynol derivatives and oxygen-, nitrogen-, and carbon-centered nucleophiles and applied to the synthesis of enantiomerically pure [3.3.1]bicyclic systems from the chiral pool. The mechanism parallels the one proposed for the hydroalkoxylation/hydroarylation sequence.



R^1 = H, Ph, 2-Br-Ph, 3-ClC_6H_4, 3-CH_3O-Ph, 4-F-Ph, 4-CH_3O-Ph, 4-CH_3-Ph, 4-CF_3-Ph, 4-NO_2-Ph
R^2 = H, COOMe

Scheme 90 $PtCl_4$ catalyzed intramolecular double alkoxylation of alkyne diols

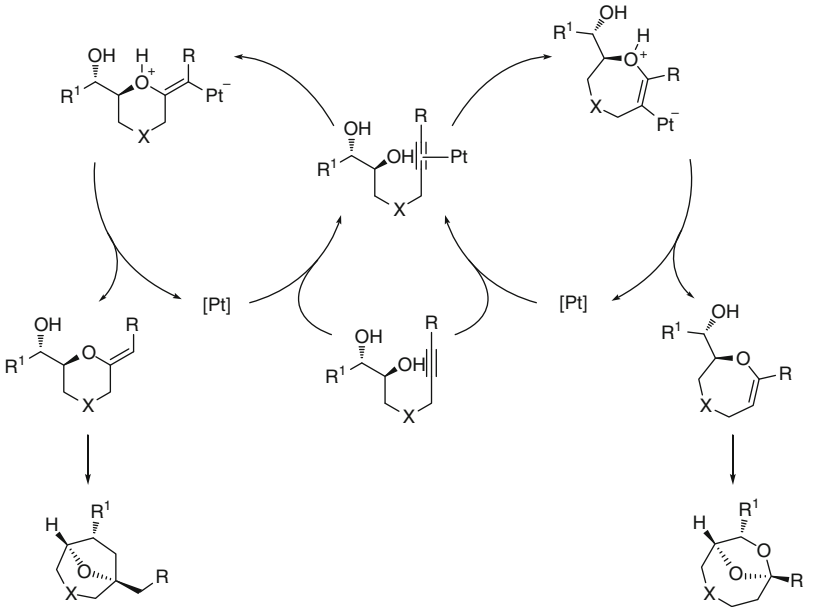
As above reported, Pt-catalyzed cycloisomerization reactions of ω-alkynols have been applied to the synthesis of oxygen-containing heterocycles and, in particular, the intramolecular nature of these transformations means that the regio- and stereoselectivities are often excellent, thus permitting the synthesis of a single compound after several bond-forming reactions. Recently, following this reasoning, a new approach to the synthesis of chiral [4.2.1]- and [3.2.1]-fused bicyclic acetals by an intramolecular double alkoxylation of alkyne diols has been reported [153] (Scheme 90).

These reactions take advantage by the fact that both enantiomers of starting diols are easily prepared in a multigram scale from glyceraldehyde or tartrate. A series of experiments with different catalysts under a number of reaction conditions was carried out. After this optimization process, the authors found that the use of 2 mol % $PtCl_4$ in THF as the solvent afforded the desired bicyclic acetals in excellent yields as single diastereoisomers after 2 h at room temperature. The course of the reaction depends on the substitution of the triple bond. Terminal alkynes give the [3.2.1]bicyclic product by a 6-*exo* pathway, whereas aryl alkynes undergo almost exclusively a 7-*endo* cyclization to give the [4.2.1]bicycles. A plausible mechanism for the double hydroalkoxylation reaction is depicted in Scheme 91. Coordination of the platinum catalyst to the alkyne provides a π-complex in which the triple bond is activated toward an intramolecular nucleophilic attack by one of the hydroxy groups. Terminal alkynes cyclize by the 6-*exo* pathway, whereas the cyclization of arylalkynes proceeds almost exclusively by the 7-*endo* pathway. Subsequent proton transfer leads to the enol ether and, finally, the corresponding fused bicyclic acetals are formed by a proton or Lewis acid catalyzed intramolecular hydroalkoxylation.

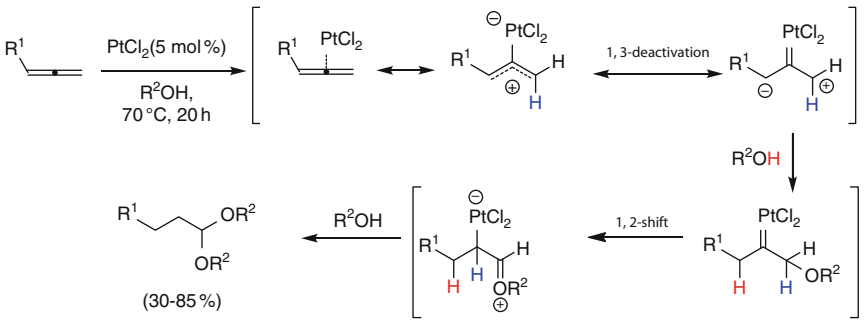
A similar approach was recently reported for the synthesis of (−)-Frontalin, (−)-*endo*-Brevicomin, and (−)-*exo*-Brevicomin [154].

7.2.3 Allenes

The intermolecular reaction of allenes with alcohols in the presence of catalytic amounts of $PtCl_2$ was recently reported by Sierra and coworkers [155]. The reaction leads to an unexpected aliphatic acetal formation by attack of two molecules of methanol to the terminal carbon of monosubstituted allene systems with complete reduction of the allene (Scheme 92).



Scheme 91 Proposed reaction mechanism for $PtCl_4$ catalyzed intramolecular double alkoxylation of alkyne diols



R^1 = cy, n-hexyl, CH_2-$CH(COOMe)_2$, CH_2-phthalimide, Ph, tolyl; R^2 = Me, Et, Bu, Bn, $(CH_2)_3$-OH

Scheme 92 Proposed mechanism for $PtCl_2$ catalyzed intermolecular double hydroalkoxylation of allenes

Into the previously reported transition-metal catalyzed intermolecular hydroalkoxylations of alkenes, gold catalysts showed to be the most active catalysts, with divergent reactivity with respect to $PtCl_2$, leading to the formation of allylethers [156]. Opposite to monosubstituted allenes, disubstituted allenes yield no aliphatic acetals. Deuteration studies support the hypothesis of a zwitterionic Pt carbene as

the key intermediate of this transformation. The key step could be seen as a formal 1,3-dipolar addition, with MeOH acting as the 1,3-dipole partner (Scheme 92).

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Gold-Catalyzed O–H Bond Addition to Unsaturated Organic Molecules

Núria Huguet and Antonio M. Echavarren

Abstract In this chapter, we review the synthetic and mechanistic aspects of addition reactions of water and alcohols to alkynes, alkenes, and allenes in the presence of gold catalysts. In addition, gold-catalyzed hydroxy- and alkoxycyclizations of 1, *n*-enynes ($n = 5$–7) are also covered.

Keywords 1,*n*-Enynes · Alkenes · Alkynes · Allenes · Gold catalysis

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1 Introduction

Among the wide variety of transformations catalyzed by gold(I), the most fundamental transformations have centered on the activation of alkynes, allenes, and alkenes with gold(I) complexes [1–13]. In particular, cationic complexes of gold(I)

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have been demonstrated to be the most alkynophilic amongst the electrophilic metals. Gold(I) complexes are highly selective Lewis acids with a high affinity for π-bonds, which has been rationalized based on relativistic effects, which are maximum with gold [6, 14–16].

A number of alkyne–gold complexes have been structurally characterized [17–21] and studied in solution [22–25]. Well-characterized complexes of gold(I) with alkenes are also known [26–42] and their structures have been studied in solution [38, 39, 43, 44]. The solid state structures of cationic allene–gold(I) [45] and diene–gold(I) [46] have also been determined.

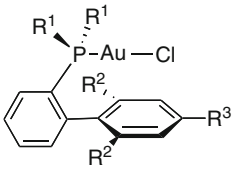
Formation of C–C bonds can be catalyzed by gold(III) salts or complexes. However, gold(III) may be reduced to gold(I) by easily oxidizable substrates [47]. The most common catalysts are cationic complexes of general formula [Au(S)(L)]X, which are formed by chloride abstraction from neutral complexes Au(L)Cl. Thus, precatalyst $Au(PPh_3)Cl$, or similar phosphine complexes, reacts with an equivalent of silver salt with a non-coordinating anion to generate catalysts $[Au(PPh_3)(S)]X$ (S = solvent or substrate molecule) [48, 49]. Cationic complex $[Au(PPh_3)(MeCN)]SbF_6$ has been prepared as a stable crystalline solid [48]. Related cationic complexes can be obtained by cleavage of the Au–Me bond in $[Au(PPh_3)Me]$ with a protic acid [48, 50–52]. Gold–oxo complex $[(Ph_3PAu)_3O]BF_4$ [53, 54] has also been used as a catalyst [55].

Gold(I) complexes **A**–**E** with bulky biphenylphosphines are useful precatalysts in many transformations (Chart 1) [56]. More convenient are their cationic derivatives **F**–**I** [57, 58], which allow performing gold(I)-catalyzed reactions in the absence of silver(I) salts [59–62]. Related complexes **J** and **K** with bis(trifluoromethanesulfonyl) amide (NTf_2, Tf = CF_3SO_2) as a weakly coordinated ligand behave similarly in catalysis [63]. Gold complexes with highly donating N-heterocyclic ligands (NHC) [64–66] such as **L**–**O** are also good precatalysts [56, 67–71]. Cationic complexes **P** and **Q** [72] and related complexes [73, 74] as well as neutral **R** and **S** [75, 76] bearing the IMes and IPr NHC ligands are selective catalysts in many applications. Gold–hydroxy complex [Au(OH)(IPr)] can also be used as a precatalyst that is activated with Brönsted acids [77, 78]. Readily available open carbenes [79–83] and other related carbenes [20, 84–87] also give rise to selective catalysts of moderate electrophilicity. The most electrophilic catalysts are gold(I) complexes with less donating phosphite or phosphoramidite ligands [88, 89] such as complexes **T** [90] and **U** [67] with tris(2,6-di-*tert*-butylphenyl)phosphite as the ligand.

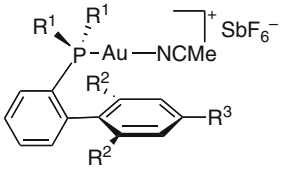
2 Gold-Catalyzed Hydrofunctionalization of π-Bonds

2.1 Hydration and Hydroalkoxylation of Alkynes

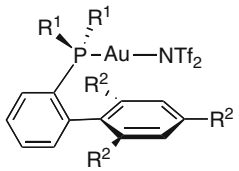
The addition of water to alkynes (hydration) is one of the fundamental methods for generating carbonyl compounds from unsaturated hydrocarbon precursors



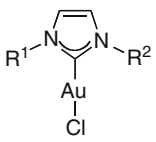
A : R^1 = Cy, R^2 = R^3 = H
B : R^1 = *t*-Bu, R^2 = R^3 = H
C : R^1 = *t*-Bu, R^2 = R^3 = *i*-Pr
D : R^1 = Cy, R^2 = OMe, R^3 = H
E : R^1 = Cy, R^2 = R^3 = *i*-Pr



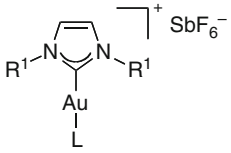
F: R^1 = Cy, R^2 = R^3 = H
G: R^1 = *t*-Bu, R^2 = R^3 = H
H: R^1 = *t*-Bu, R^2 = R^3 = *i*-Pr
I: R^1 =Cy, R^2 = OMe, R^3 = H



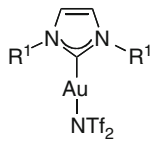
J: R^1 = *t*-Bu, R^2 = H
K: R^1 =Cy, R^2 = *i*-Pr



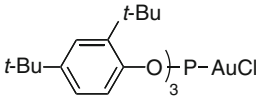
L: R^1 = R^2 = 2,4,6-Me_3 C_6 H_2
M: R^1 = 2,4,6-$Me_3C_6H_2$, R^2 = Me
N: R^1 = R^2 = Me
O: R^1 = R^2 = 2, 6-*i*-$Pr_2C_6H_3$



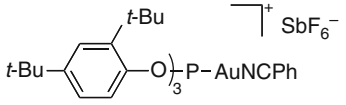
P: R^1 2, 4, 6-$Me_3C_6H_2$,
L = 2, 4, 6-$(MeO)_3C_6H_2CN$
Q: R^1 = 2, 6-*i*-$Pr_2C_6H_3$,
L = PhCN



R: R^1 = 2, 4, 6-$Me_3C_6H_2$
S: R^1 = 2, 6-*i*-$Pr_2C_6H_3$



T



U

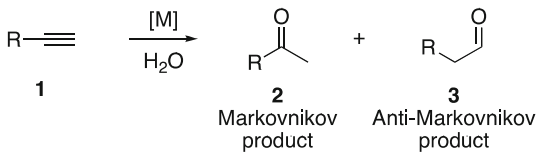
Chart 1 Gold(I) catalysts with bulky phosphine, *N*-heterocyclic carbene (NHC), or phosphite ligands

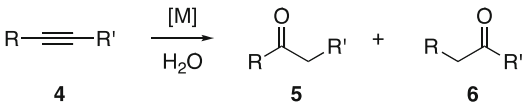
[1, 91–96]. This transformation is a highly atom-economical process that does not involve energy-intensive redox chemistry.

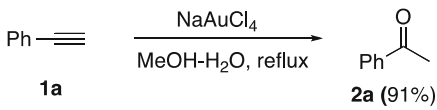
The first hydration of an alkyne was discovered in 1881 by Mikhail Kucherov, a Russian chemist from the Imperial Forestry Institute in St. Petersburg, using mercury(II) bromide as the catalyst [97] producing acetaldehyde. This reaction has been extensively applied in synthesis, although due to the toxicity of mercury compounds and the relatively low turnover numbers (<500), much effort has been done to find new catalysts. Thus, transition-metal-complexes containing Pd (II) [98], Pt(II) [99], Ru(II) [100], Rh [101], and other metal centers [91] have been used, although in most cases the catalytic efficiency was only moderate.

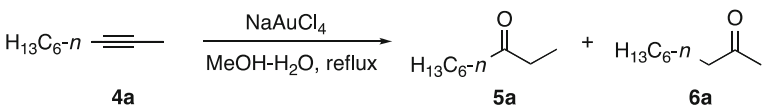
The hydration of terminal alkynes gives either a methyl ketone **2** (Markovnikov addition) or an aldehyde **3** (anti-Markovnikov addition), whereas unsymmetrical internal alkynes can give two regioisomeric ketones (Scheme 1) [91]. The catalytic addition of water with ruthenium(II)-complexes described by Tokunaga and Wakatsuki [100, 102] gives rise to anti-Markovnikov hydration. On the other hand, the Markovnikov selectivity is observed in most alkyne hydrations in the

Scheme 1 General scheme of alkyne hydration









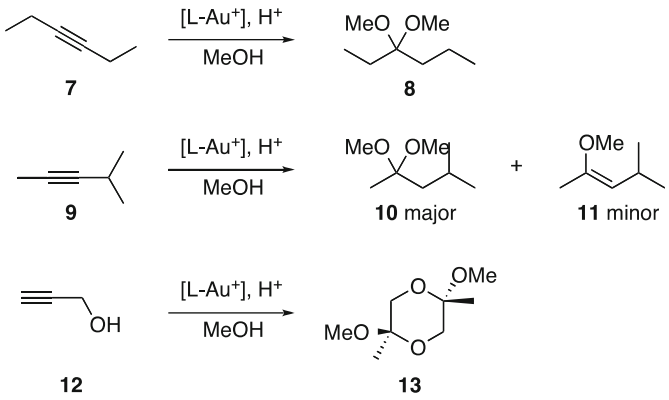
(94%, 40:60 ratio)

Scheme 2 Hydration of alkynes catalyzed by $NaAuCl_4$

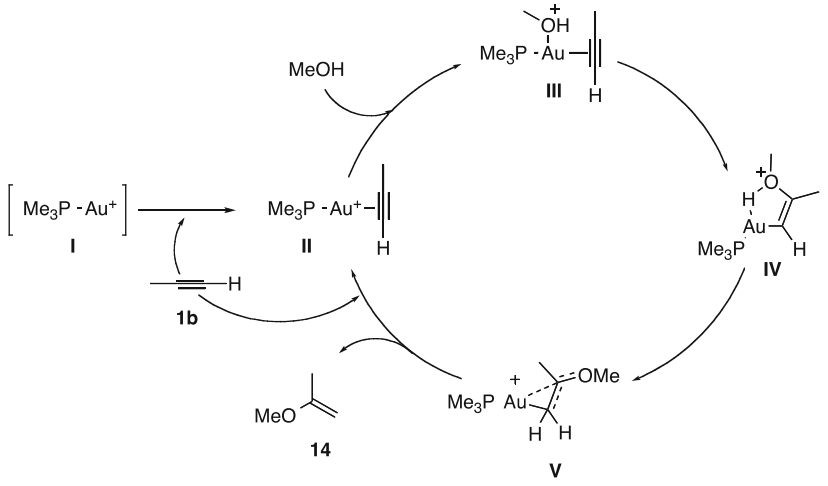
presence of electrophilic salts or complexes of Cu(II) [103], Ag(I) [103], Pt [99], Rh [101], and Pd(II) [98].

The first hydration of alkynes with a gold(III) catalyst ($HAuCl_4$) was reported in 1976 by Thomas [104]. The original procedure using MeOH under reflux for 24 h was modified by Fukuda and Utimoto in 1991 [105] using $NaAuCl_4$ as the catalyst. Terminal alkynes were smoothly hydrated to afford the corresponding ketones, whereas internal alkynes provided mixtures of ketones with poor regioselectivity (Scheme 2).

Teles and co-workers proposed in 1998 a generally useful catalytic process for the addition of heteronucleophiles to alkynes, making possible the addition of weak nucleophiles to unactivated alkynes [50, 106]. Cationic gold(I) complexes of the general type [L–Au^+] (where L is a phosphine, a phosphite, or an arsine) generated in situ were used as catalysts. The addition of alcohols to alkynes (hydroalkoxylation) occurs under mild conditions in the presence of an acidic co-catalyst. A Lewis acid such as boron trifluoride can also be utilized because it is rapidly hydrolyzed to trimethyl borate and HF under the reaction conditions. Internal symmetrical alkynes such as **7** give **8** as the only product (Scheme 3), while in the case of unsymmetrical alkynes such as **9**, the addition takes place at the less sterically hindered carbon leading to acetal **10** as the major product together with smaller amounts of enol ether **11**. Terminal alkynes are also suitable substrates and propargyl alcohols also react readily under these conditions.



Scheme 3 Addition of alcohols to symmetric and asymmetric alkynes



Scheme 4 Proposed mechanism for the addition of MeOH to propyne catalyzed by trimethylphosphine gold(I) cation

Unlike in the case of $[M(CO)_6]$ (M = Cr, Mo, W) and certain Ru(II) complexes, which activate alkynes via vinylidene metal complexes [102, 107–111], gold complexes promote reactions of alkynes by the formation of electrophilic η^2-alkyne–gold(I) complexes [1–13].

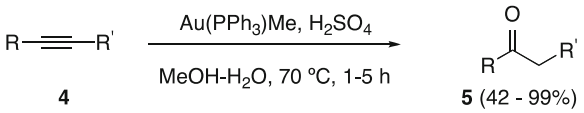
The mechanism initially proposed for the catalytic addition of alcohols to alkynes starts with the coordination of the alkyne to the cationic gold(I) complex **I**, generated by protonolysis of a methylgold complex LAuMe (Scheme 4). The gold (I)–propyne complex (**II**) is then attacked by a molecule of methanol to give intermediate **III** by a *syn*-addition involving activation of both methanol and the alkyne by LAu^+. Rearrangement of **III** to **IV** (the *Z* isomer) followed by another rearrangement produces intermediate **V**. A ligand exchange regenerates complex **II**

and gives the final hydroalkoxylated product. The addition of water to alkynes is often selective, even in the presence of excess of alcohol or carboxylic acid. More recently, a theoretical study by Hashmi and Schwerdtfeger on the addition of water to propyne catalyzed by $AuCl_3$ was consistent with an anti-addition of water to the alkyne activated by Au(III) [112].

Hayashi and Tanaka et al. reported in 2002 that the Au(I)-acid catalytic system in aqueous methanol was a powerful catalyst, affording the corresponding Markovnikov hydration product of a large variety of alkynes (Scheme 5) with turnover frequencies of at least two orders of magnitude higher than those obtained using [*cis*-$PtCl_2(tppts)_2$] [51, 113].

The efficiency of the catalyst was significantly enhanced by the addition of appropriate ligands (CO and $(PhO)_3P$), which enable us to minimize the amount of the precious catalyst (Table 1, entries 2 and 3). The reaction did not proceed in the absence of either the Au catalyst or sulfuric acid. Other acid co-catalyst such as CF_3SO_3H (entry 4), CH_3SO_3H (entry 5), and $H_3PW_{12}O_{40}$ (entry 6) also gave very high yields even in the absence of the coordinative additives. The use of solvents such as dioxane, acetonitrile, THF, DMF, dichloromethane, or 2-propanol resulted in lower yields. 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 exclusively Markovnikov products. Internal alkynes displayed lower reactivity, presumable because of steric hindrance.

Catalytic hydration of phenylacetylene has been accomplished in a biphasic mixture of ionic liquids and toluene using [BMTz] [$AuCl_3Br$] **15** as a catalyst (Scheme 6) [114]. Several imidazolium derived ionic liquids, as well as **15**, can be



R^1 = Alkyl, vinyl, Ar, hydroalkyl, $NC(CH_2)_3$, $Cl(CH_2)_3$
R^2 = H, Me, Pr^n, Ph

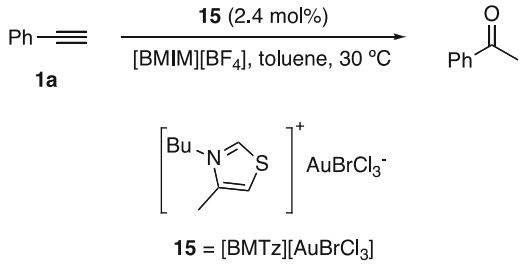
Scheme 5 Au(I)-acidic catalytic hydration of alkynes in aqueous methanol

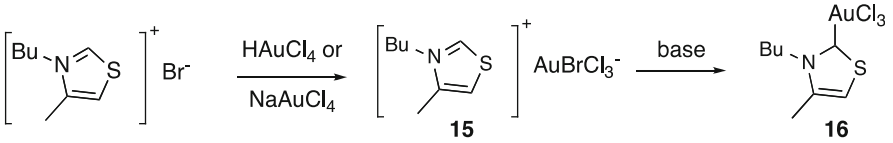
Table 1 Hydration of 1-octene in methanol

Entry	Acid	Additive	Yield[a] (%)
1	H_2SO_4	–	35
2	H_2SO_4	CO (1 atm)	99
3	H_2SO_4	$(PhO)_3P$ (0.004 mmol)	90
4	CF_3SO_3H	–	99
5	CH_3SO_3H	–	77
6	$H_3PW_{12}O_{40}$	–	80

[a]GC yield of 2-octanone

Scheme 6 Gold-catalyzed hydration of phenylacetylene in an ionic liquid





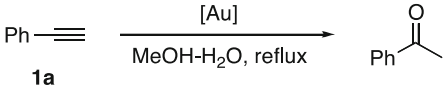
Scheme 7 Synthesis of gold–carbene complexes **16** from imidazolium derived ionic liquid **15**

Table 2 Hydration of phenylacetylene with organic Au(III) or Au(I) compounds

Entry	Catalyst	Cat. loading (mol%)	Acid	Time (h)	Conversion (%)	Yield (%)
1	$[Au(C_6F_5)Cl_2]$	4.5	–	1.5	100	98
2	$[Au(C_6F_5)Cl_2(tht)]$	2	–	1.5	0	–
3	$BzPPh_3[Au(mes)Cl_3]$	2	–	1.5	72	70
4	$t\text{-}NBu_4[Au(C_6F_5)Br_2]$	2.5	–	4	96	90
5	$t\text{-}NBu_4[Au(C_6F_5)Cl_2]$	0.5	H_2SO_4	1.5	100	–
6	$[Au(Me)PPh_3]$	1	H_2SO_4	1.5	100	–
7	$[Au(Me)PPh_3]$	0.5	HSO_3CF_3	1.5	100	–

converted into gold–carbene complex **16** by sequential deprotonation and coordination, opening the way for in situ catalyst design (Scheme 7).

Anionic and neutral organometallic gold(III) compounds with one or two organic radicals, C_6F_5 or $(2,4,6\text{-}(CH_3)_3C_6H_2)$, can efficiently mediate alkyne hydration in neutral media in refluxing methanol with a catalytic activity similar to that reported for $NaAuCl_4$ (Table 2) [115]. The addition of acidic co-catalysts improves the catalytic activity of this reaction.



The active organometallic gold(III) catalysts in the hydration of phenylacetylene proved to be also efficient catalysts for the addition of MeOH giving the enol ether **17** and the acetal **18** (Table 3).

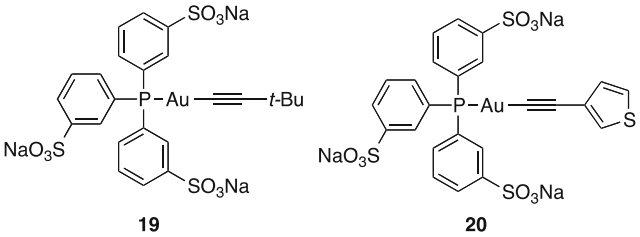


Fig. 1 Water soluble gold(I)–alkynyl complexes

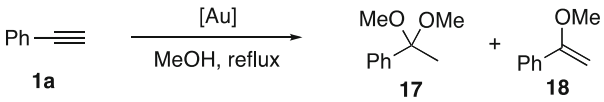


Table 3 Addition of anhydrous methanol to phenylacetylene with organometallic gold(III) compounds

Entry	Catalyst	Cat. loading (mol%)	Time (h)	Conversion (%)	Yield[a] (%)
1	$BzPPh_3[Au(mes)Cl_3]$	3	1.5	**17** (26) + **18** (64)	–
2	$BzPPh_3[Au(C_6F_5)Cl_3]$	3	1.5	**17** (45) + **18** (55)	–
3	$BzPPh_3[Au(C_6F_5)_2Cl_2]$	2.5	1.5	**17** (100)	98

[a]Isolated yield

Water-soluble phosphine ligands TPPMS, TPPDS, and TPPTS (mono-, di-, and tri-sulfonated triphenylphosphine, respectively) were tested as ligands for the hydration of alkynes in aqueous media [116]. Complexes **19** and **20** (Fig. 1) gave the highest turnover frequencies ever reported (1,000 and 1,060 h^{-1}, respectively) for the hydration of phenylacetylene under optimum conditions (0.1 mol% catalyst loading, 10 mol% H_2SO_4, reflux, and $MeOH/H_2O$).

Gold(I) complexes such as $AuSPhosNTf_2$ having *N*-phenyltriflimide ligand are efficient catalysts for the hydration of a wide range of alkynes to the corresponding ketones with no acidic co-catalyst required ([117]; for regioselective transformation of alkynes into cyclic acetals with gold(I) catalyst see [118]). Complexes of this type allow us to perform hydrations of alkynes under milder, more selective, and operationally easier conditions. Alkyl and aryl terminal alkynes, internal alkynes, and propargylic alcohols, including enantiopure compounds, are cleanly transformed into the corresponding ketones in nearly quantitative yields.

The first gold(I)–carbene complex with a gold–oxygen bond $[Au(R_2\text{-imy})OC(O)CH_3]$ (Fig. 2) was successfully applied for the addition of water to 3-hexyne in the presence of a Lewis acid as a co-catalyst [115].

Formation of α,β-unsaturated carbonyl compounds from propargylic alcohols was described in 2007 by Chung et al. [119] and from propargylic acetates by Nolan and co-workers (Scheme 8) with $[(NHC)Au^I]$ complexes [120]. The presence of water was required for the formation of the desired products. Steric hindrance of the ligand appeared to be crucial for the selectivity of the reaction. The reaction was not

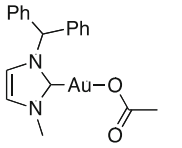
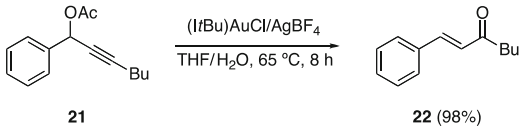
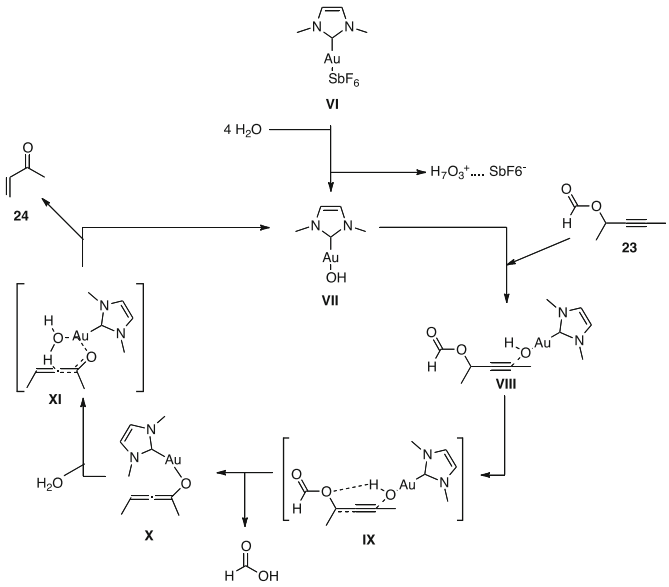


Fig. 2 Gold(I)–carbene complex: [Au(R_2-imy)OC(O)CH_3]

[Au(R_2-imy)OC(O)CH_3]



Scheme 8 Gold-catalyzed formation of α,β-unsaturated ketones with NHC ligands



Scheme 9 Proposed mechanism for the gold-catalyzed formation of α,β-unsaturated carbonyl compounds based on calculations

affected by aromatic substitution, and cinnamyl ketones possessing neutral, electron-withdrawing and electron-donating groups were obtained in excellent yields. However, acetylenes with bulky groups such as TMS were not substrates for this reaction. Similar transformations were reported by Engel and Dudlye [121] using an Au(III)-catalyzed Meyer–Schuster rearrangement, and Akai et al. [122] where the combination of cationic Au catalysts with $MoO_2(acac)_2$ leads to the 1,3-rearrangement of propargyl alcohols.

The proposed reaction mechanism for the gold-catalyzed production of α,β-unsaturated carbonyl compounds based on calculations is presented below (Scheme 9). Gold(I) activates water by forming the hydroxide complex **VII** and

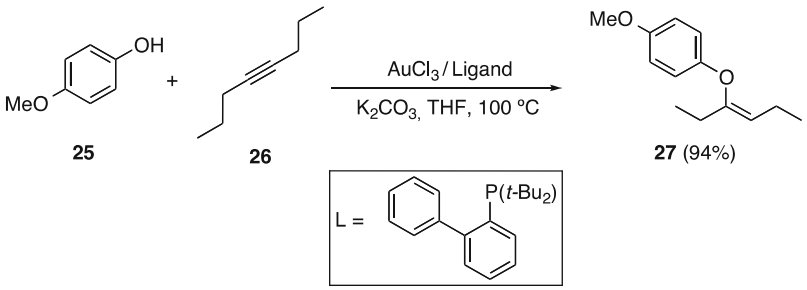
releases a solvated cluster of $HSbF_6$. The proton of the hydroxy group of **VII** is transferred to the inner oxygen atom of **23** and the oxygen atom binds in a concerted process to the most electron-deficient carbon atom of the triple bond. Formic acid is formed and acts as a leaving group. To complete the catalytic cycle, water adds to **IX**, proceeding through a cyclic six-membered ring TS (**XI**), to give the enone **24** and regenerating the catalyst.

Two years later, the group of Nolan succeeded in decreasing the catalyst loading to parts-per-million (typically 50–100 ppm and as low as 10 ppm) under acid-free conditions with the same NHC–gold(I) complexes [123].

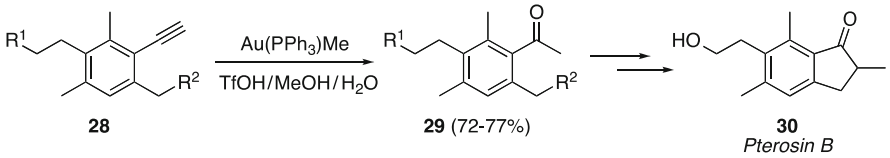
Synthesis of diverse aryl vinyl ethers is possible through gold-catalyzed intermolecular addition of substituted phenols to unactivated alkynes (Scheme 10) [124].

Gold-catalyzed hydration of alkynes has been applied in the total synthesis of pterosines B and C (Scheme 11) [125], a class of sesquiterpene indane derivative that possesses interesting biological activity.

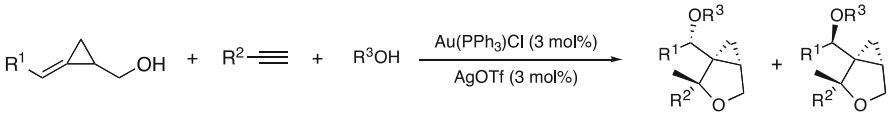
A three-component addition for the hydration of alkynes was accomplished to form efficiently 3-oxabicyclo[3.1.0]hexanes from 2-(arylmethylene)cyclopropylcarbinols, terminal arynes, and alcohols (Scheme 12) [126].



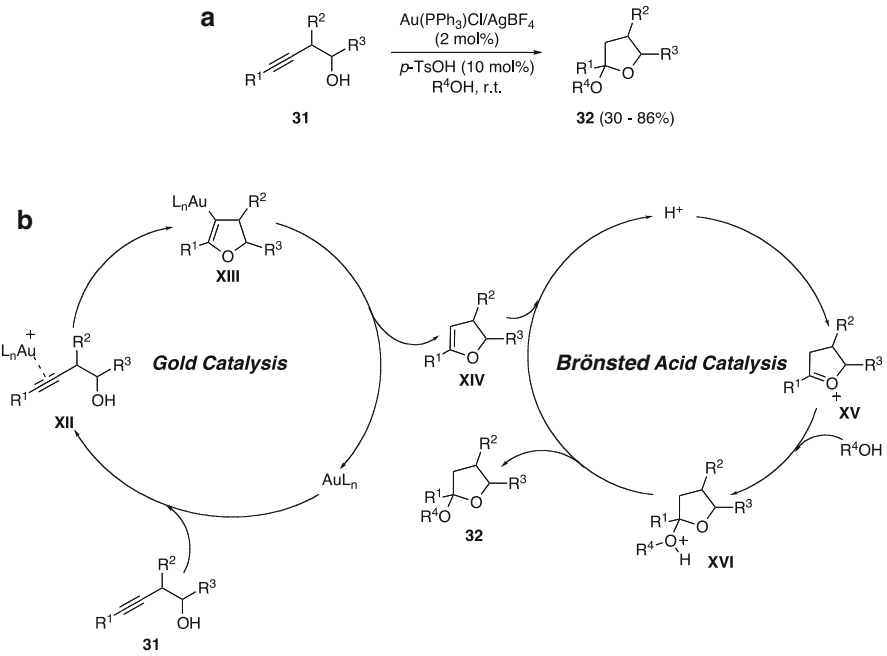
Scheme 10 Hydrophenoxylation of alkynes with $AuCl_3$



Scheme 11 Application of alkyne hydration to total synthesis

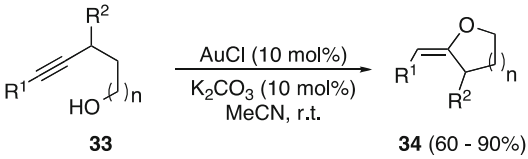


Scheme 12 Hydration of alkyne via three-component addition methodology



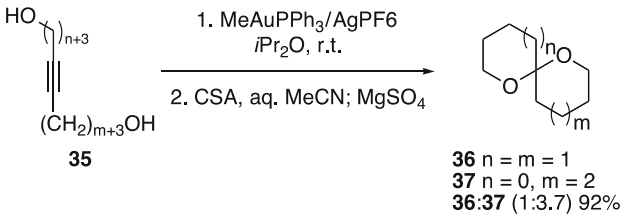
Scheme 13 (**a**) Gold- and acid-catalyzed synthesis of tetrahydrofuranyl ethers **32**. (**b**) Proposed mechanism for the intramolecular hydroalkoxylation of **31**

Scheme 14 Formation of α-alkylidene oxolanes and oxanes catalyzed by gold chloride and base



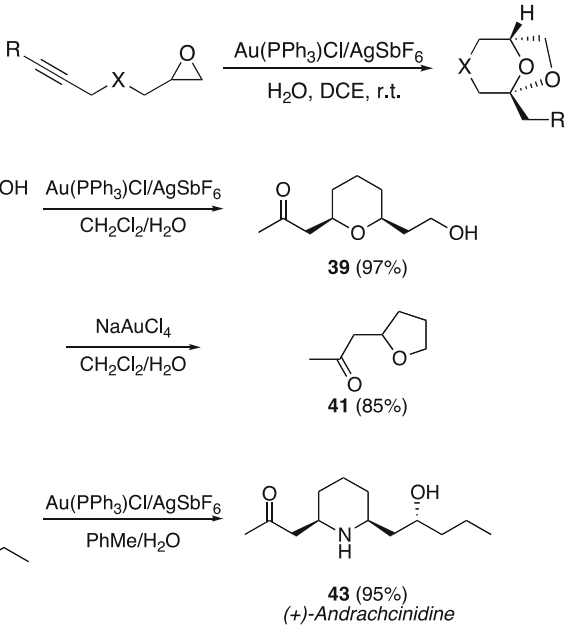
An intramolecular version of alkyne hydration was reported in 2006 by Belting and Krause [127] providing an efficient route to tetrahydrofuranyl ethers **32**. This transformation consists in a tandem cycloisomerization–hydroalkoxylation of homopropargylic alcohols **31** in the presence of an alcohol in a dual catalyst system (a gold precatalyst and a Brönsted acid) under mild conditions (Scheme 13). The reaction proceeds satisfactorily with terminal and internal alkynes, with bis-homopropargylic alcohols and alkynyl phenols to provide cyclic acetal skeletons that occur in a variety of natural products. Substituted furanones can be obtained by gold(III)-catalyzed activation of alkynes by heterocyclization and subsequent 1,2-alkyl shift [128].

The intramolecular addition of a hydroxyl group to a triple bond has found many synthetic applications. ω-Acetylenic alcohols **33** have been regio- and stereoselectively converted to the corresponding α-alkylidene oxygenated heterocycles in the presence of catalytic amounts of AuCl and K_2CO_3 (Scheme 14) [129].



Scheme 15 Gold-catalyzed hydroalkoxylation of 4-alkynol **35**

Scheme 16 Gold(I)-catalyzed addition of water to alkynyl epoxides



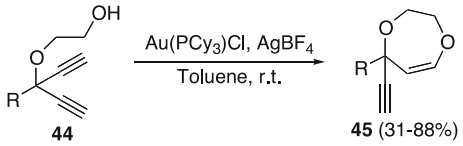
Scheme 17 Gold-catalyzed synthesis of oxygen- and nitrogen-containing heterocycles from alkynyl ethers

Moreover, spiroketals are produced from tandem hydroalkoxylation of 4-alkynols (Scheme 15) [130]. Starting from diynediols, bis-spiroketals are obtained using Au (I) as catalysts [131]. Furthermore, Barluenga et al. reported the formation of spirocyclic compounds in a tandem alkyne hydroalkoxylation [4 + 2] cycloaddition reaction [132, 133], together with a tandem intramolecular hydroalkoxylation of a triple bond followed by a Prins-type cyclization [129].

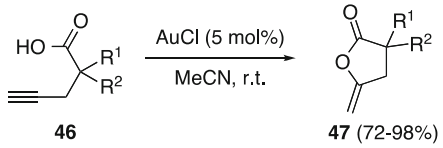
Acetal skeletons are also obtained as products through a highly regio- and diastereoselective intermolecular addition of water and alcohols to alkynyl epoxides catalyzed by gold(I) (Scheme 16) [134, 135].

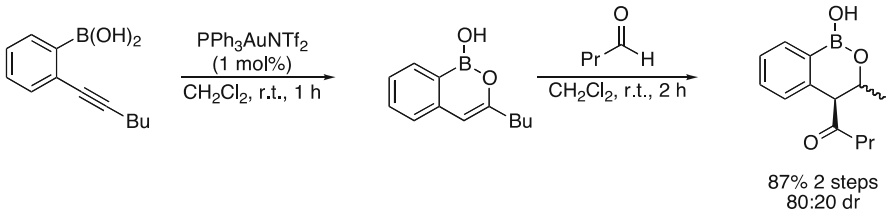
Additionally, homopropargylic ethers with pendant nucleophiles, when subjected to gold catalysts in an aqueous solvent, provide heterocyclic ketones (5- and 6-membered rings) (Scheme 17) [136, 137]. This method was applied to the formation of piperidines

Scheme 18 Cyclization of diynols to dioxepine derivatives



Scheme 19 Intramolecular addition of carboxylic acids to alkynes





Scheme 20 Gold-catalyzed boron enolate formation/aldol reaction

and to the efficient enantioselective synthesis of (+)-andrachcinidine (**43**). Synthesis of indenyl ethers by gold(I)-catalyzed intramolecular carboalkoxylation of alkynes was reported by Dubé and Toste [138]. Recently, Renault et al. have reported an intramolecular gold(I)-catalyzed addition of ethers to alkynes followed by a carbode-metallation giving access to a substituted chromone derivatives [139].

Intermolecular hydroalkoxylation of alkynes is also possible by hydration of propargyl acetates assisted by a neighboring carbonyl group [140] and with *N*-Boc-protected carbamates [141].

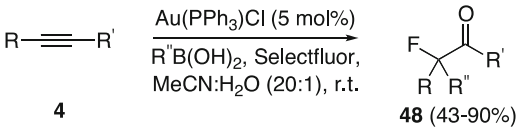
Carbocyclization of 1,5- and 1,6-diynes has been reported leading to benzopyrones [142] and *Z*-cyclopentylidenes [143, 144], respectively. Furthermore, 1,4-diynes **44** react in the presence of gold-catalysts to form seven-membered ring heterocycles **45** by an *endo*-cyclization (Scheme 18) [145].

Carboxylic acids also react with alkynes in the presence of gold(I) catalysts to form lactones [146, 147]. AuCl catalyzes the conversion of substrate **46** to **47** at room temperature without additives (Scheme 19). Six-membered lactones can be formed in the presence of AuCl and K_2CO_3 [147]. The corresponding esters can be used instead of carboxylic acids [148, 149].

Boronic acids react intramolecularly with alkynes in the presence of PPh_3AuNTf_2 as a catalyst to form synthetically useful boron enolates in excellent yields (Scheme 20) [150].

The transition-metal-catalyzed hydration of alkynes and related reactions adds the elements of H_2O or ROH to the alkyne. Recently, Hammond and co-workers expanded these procedures further by Selecfluor in combination with a boronic

Scheme 21 Fluoro functionalized hydration of alkynes



acid, leading to product **48** (Scheme 21) [151]. Related examples of gold-catalyzed oxidative alkene alkoxylations in the presence of Selectfluor and boronic acid have been reported by Zhang et al. [152] and Toste et al. [153, 154].

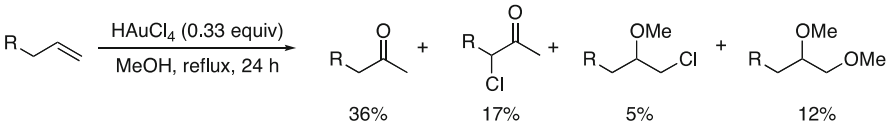
Hydroamination of alkynes using gold catalysts has also attracted considerable interest [155–158]. In this context, triazole–Au(I) complexes, which show improved thermal stability, are active catalysts for the hydroamination of alkynes [159]. The hydrothiolation of alkynes using soluble and heterogenized gold complex catalysts was reported by Corma and co-workers [160].

2.2 *Hydroalkoxylation of Alkenes*

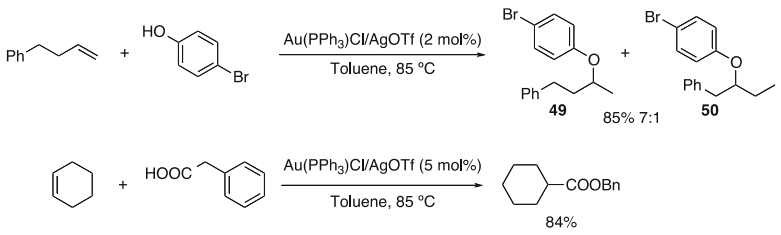
Despite the successes of the gold-catalyzed addition of O-nucleophiles to alkynes, the corresponding catalyzed reactions involving nucleophilic addition to olefins are very limited. Mild, metal-catalyzed additions of O–H bonds across olefins have been studied for decades, and efforts to develop such processes have intensified in the last years. Results of the hydroalkoxylation of alkenes are collected in different reviews [1, 94–96, 161].

The pioneer experiments on the hydroalkoxylation of alkenes were carried out by Thomas et al. (1976, [162]) using $HAuCl_4$ in MeOH, following the previous reported work on the oxidation of alkenes by mercury(II), thalium(III), and lead(IV) salts (1974–1975) [163, 164]. Mixtures of ketones, α-chloroketones, 1-chloro-2-methoxyalkanes, and 1,2-dimethoxyalkanes were obtained in most of the cases (Scheme 22).

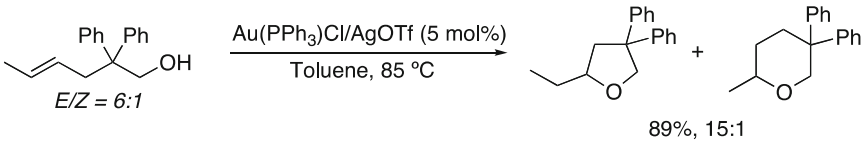
The first important contribution in this field was reported by Yang and He [165]. The intermolecular addition of phenols and carboxylic acids to internal and terminal alkenes was applied successfully in the presence of $Au(PPh_3)Cl$ combined with AgOTf in toluene to give good yields of the Markovnikov products (Scheme 23). Differently substituted olefins and both electron-rich and electron-withdrawing phenols are good substrates for this addition reaction. Hydroxylation of unactivated olefins can also be achieved combining gold(I) and electron deficient phosphine ligands in the presence of alcohol substrates bearing halogen or alkoxy groups as additional coordination sites [166]. The intramolecular cyclization of γ-hydroxylalkene can be mediated by gold(I) under the same conditions (Scheme 24).



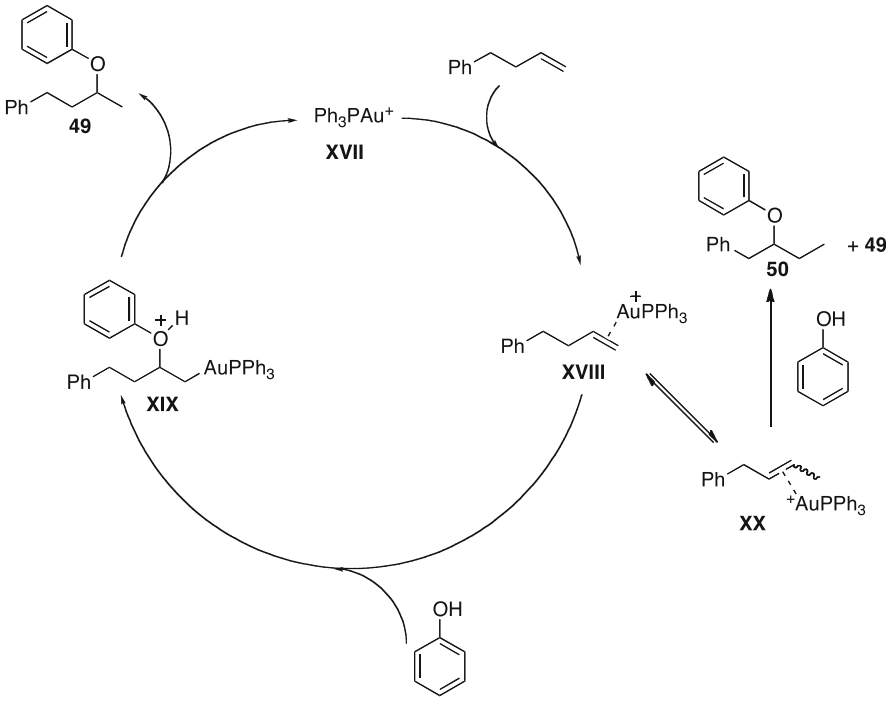
Scheme 22 Oxidation of alkenes with gold(III)



Scheme 23 Gold(I)-catalyzed intermolecular addition of phenols and carboxylic acids to alkenes



Scheme 24 Cyclization of hydroxy alkenes



Scheme 25 Proposed catalytic mechanism of intermolecular addition of phenols and carboxylic acids to alkenes

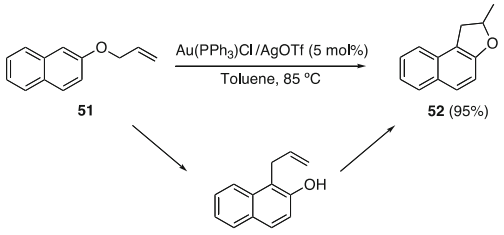
The reaction mechanism for the intermolecular addition of phenols to alkenes is proposed in Scheme 25. Cationic gold(I) catalyst binds and activates alkene for a nucleophilic addition by the phenols or carboxylic acids, a reaction reminiscent of

the first step to the Wacker process catalyzed by palladium(II). A subsequent proton-transfer step affords the final product **49** and regenerates gold(I) catalyst. The gold catalyst also promotes migration of double bonds, which gives rise to formation of small amounts of side product **50**.

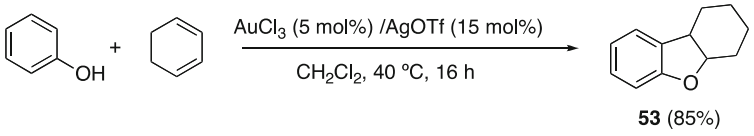
However, caution should be exercised at interpreting these transformations as genuine metal-catalyzed reactions since it has been demonstrated that intermolecular additions of the O–H bonds of phenols and alcohols to olefins can be catalyzed by 1 mol% of triflic acid formed by hydrolysis of metal triflates [167, 168]. The same applied to the addition of the N–H bond of sulfonamides and benzamides.

The same catalytic system was used to prepare dihydrobenzofurans **52** from aryl allyl ethers **51** through an intramolecular process (Scheme 26) [169]. This reaction proceeds by a Claisen rearrangement, followed by gold(I)-catalyzed addition of the resulting phenol to the allyl group.

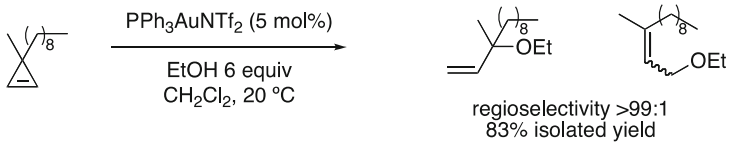
Li and co-workers extended this reaction to 1,3-dienes (Scheme 27) in an efficient gold-catalyzed intermolecular atom-economical annulation of phenols and naphthols to generate dihydrobenzofuran derivatives such as **53** [170]. The reaction involves a sequential double addition of a carbon and an oxygen nucleophile to the diene. Interestingly, gold(III) gave the best results in this transformation, whereas cationic gold(I) failed as a catalyst. Moreover, the addition of alcohols to 3,3-disubstituted cyclopropenes can be successfully applied to gold catalysis to form alkyl *tert*-allylic ethers in good yields (Scheme 28) [171].



Scheme 26 Formation of dihydrobenzofurans from aryl allyl ethers catalyzed by gold



Scheme 27 Annulation of phenol with cyclohexadiene catalyzed by gold and silver



Scheme 28 Gold(I)-catalyzed addition of alcohol to cyclopropene

Scheme 29 Addition of methanol to styrene with an $AuCl_3$–$CuCl_2$ catalyst

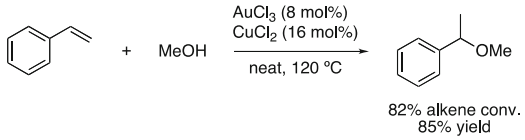
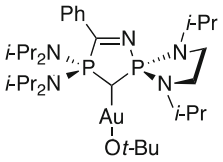
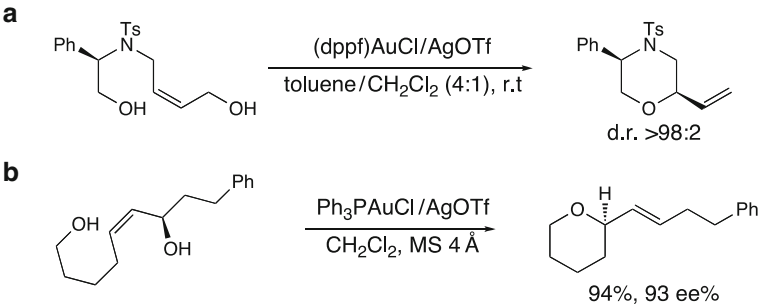


Fig. 3 Cyclic carbodiphosphorane–Au(I) complex





Scheme 30 Chirality transfer in Au-catalyzed cyclization reaction of allylic diols

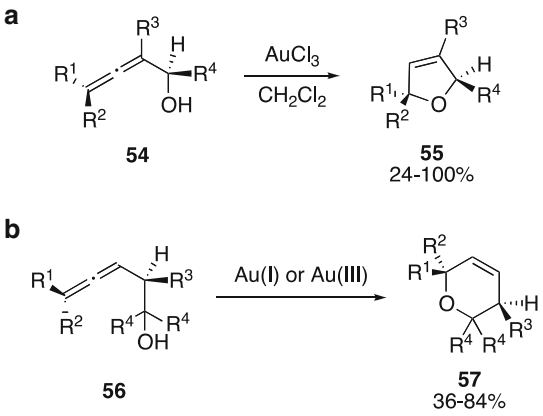
Zang and Corma [172, 173] reported the intermolecular addition of alcohols to alkenes combining gold(III) catalyst with catalytic amounts of $CuCl_2$ salt under relatively harsh conditions. It was proposed that the role of $CuCl_2$ in these gold (III)–$CuCl_2$ catalysts is to stabilize the cationic Au(III) (Scheme 29).

Gold(I) complexes bearing bulky cyclic carbodiphosphorane ligands (Fig. 3) showed for the first time to be active in the hydroalkoxylation of acrylonitrile yielding the anti-Markovnikov product [174].

Recently, Bandini and co-workers [175] reported an intramolecular gold(I)-catalyzed asymmetric nucleophilic alkoxylation of allylic alcohols leading to vinyl-substituted six- and seven-membered heterocycles (Scheme 30a). Following this work, Aponick and Biannic [176] developed a synthesis of tetrahydropyrans in high enantio- or diastereoselectivities (Scheme 30b). The configuration of the allylic alcohol controls efficiently the facial selectivity when the substrates include additional stereocenters.

2.3 Hydration and Hydroalkoxylation of Allenes

Hydration of allenes catalyzed by gold has been much less studied. The interest of the addition of primary and secondary alcohols to allenes using gold complexes



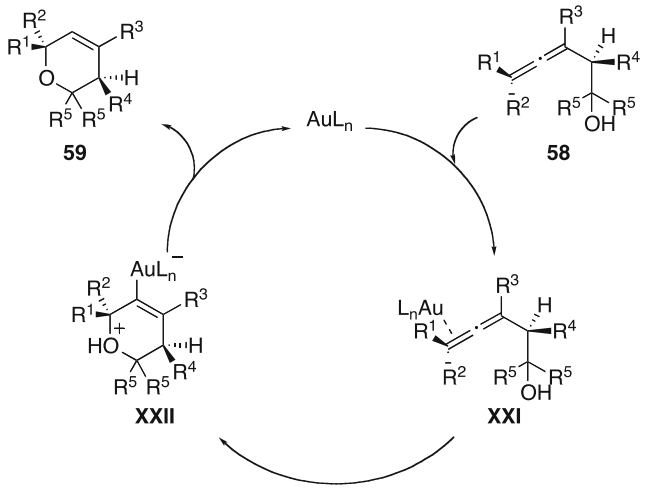
Scheme 31 (**a**) Electrophilic cyclization of α-hydroxyallenes **54** to 2,5-dihydrofurans **55**. (**b**) Gold-catalyzed cycloisomerization of β-hydroxyallenes **56** to dihydropyrans **57**

[1, 94–96, 161] started in the twenty-first century. Hoffmann-Röder and Krause (2001) investigated the gold(III)-catalyzed cyclization reactions of allenyl carbinols **54** to form 2,5-dihydrofurans **55** (Scheme 31) by using 5–10 mol% of the catalyst [177], since it was known that catalytic amounts of Au(III) induce the cyclization of allenyl ketones to furans [178]. All the reactions proceeded under perfect stereocontrol. The use of gold(III) chloride, compared to the established Ag(I)-promoted method [179], allowed the transformation of notoriously difficult substrates and increased the reaction rate. Similar reactions of allenyl carbinols were reported by Hashmi et al. [180] providing evidence for a mechanism of an in situ reduction of gold (III). Hyland and Hegedus [181] developed an efficient hydrocyclization of alleneamides mediated by *N*-iodosuccinimide yielding similar dihydrofurans. Recently, the groups of Lipshutz and Krause have found that these heterocyclizations can efficiently be carried out with $AuBr_3$ in an aqueous micellar system using poly(oxyethyl)-α-tocopheryl sebacate as the amphiphile [182].

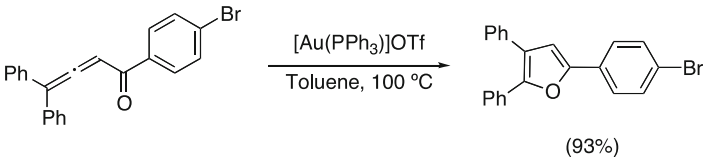
The group of Krause [183, 184] extended this methodology to the Au(I) and Au (III) 6-*endo*-cyclization of β-hydroxyallenes **58** to dihydropyrans **59** in good chemical yields (Scheme 31). The chirality transfer can be explained with the mechanistic model shown in Scheme 32. Thus, coordination of the gold catalyst to the terminal double bond of the allene **58** gives rise to the formation of the intermediate **XXI**, which is transformed into the σ-gold complex **XXII** by nucleophilic attack of the oxygen. Protodemetalation of the latter intermediate provides the hydropyran **59** and releases the gold catalyst. More recently, the same group combined the lipase-catalyzed kinetic resolution of racemic α-allenic acetates with gold-catalyzed cycloisomerization to form the corresponding 2,5-dihydrofuranes in one pot [185].

The cyclization of allenols was applied successfully to the synthesis of different natural products (Krause 2007): (−)-isocyclocapitelline [186], (−)-isochrysotricine [186], and furanomycin derivatives [187].

Similar intramolecular *exo*-hydrofunctionalizations of γ-allenes were achieved by Widenhoefer et al., with Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl activated by either AgOTf



Scheme 32 Proposed mechanism for the cyclization of β-hydroxyallenes to dihydropyrans



Scheme 33 Gold-catalyzed [1,2]-alkyl shift in allenyl ketones

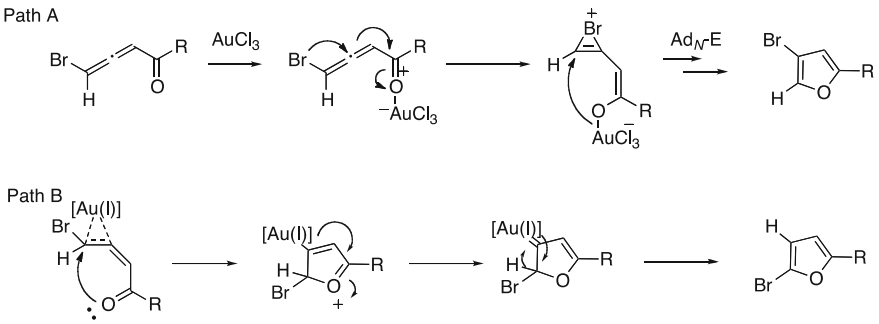
or AgOTs with transfer of chirality from the allene to the newly formed stereogenic center [188, 189]. An enantioselective cyclization was achieved in the presence of Au_2 complexes of the form $[Au_2(P–P)Cl_2]$ (P–P = 2,2′-bis(diarylphosphino)biphenyl) activated by AgOTs [188]. Toste et al. reported a powerful chiral counterion strategy for asymmetric gold hydroalkoxylation of allenes [190] improving the enantioselectivity reported with chiral ligands. Examination of solvents demonstrated that more-polar solvents, such as nitromethane or acetone, gave significantly lower enantiomeric excess values than THF or benzene. Recently, the same group demonstrated that gold–phosphine complexes can be readily encapsulated in a tetrahedral Ga_4L_6 [L = *N*,*N*′-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene] cluster in both methanol and water, improving the catalytic activity of Me_3PAuBr in the hydroalkoxylation of allenes [191].

Hydrofunctionalization of allenes also can be promoted by ketones in the presence of $[Au(PPh_3)]OTf$ to form furans [192]. This gold-catalyzed synthesis of furans proceeds by a novel [1,2]-alkyl shift (Scheme 33). Gold(III) porphyrin-catalyzed cycloisomerization of allenones gave the corresponding furans in good to excellent yields (up to 98%) [193].

Haloallenyl ketones cyclization gives halofuranes via two competitive pathways depending on the catalyst (Scheme 34) [194]. Thus, more oxophilic Au(III) activates the carbonyl group leading to 3-halofurans by a 1,2-halogen shifts, whereas Au(I) selectively activates the terminal double bond of the allene to form 2-halofurans.

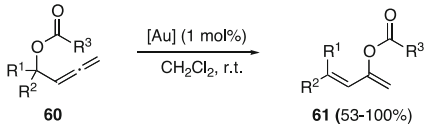
Allenyl carbinol esters **60** (Scheme 35) form 1,3-butadien-2-ol esters **61** under mild conditions with low catalyst loadings and good *E*-selectivity [195]

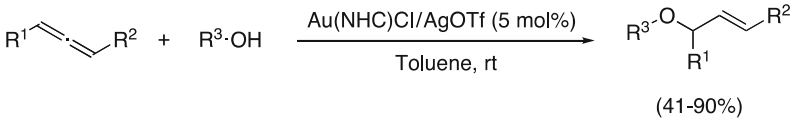
The intermolecular hydroalkoxylation of allenes was reported by Widenhoefer et al. catalyzed by a gold(I) *N*-heterocyclic carbene complex and AgOTf providing a straightforward entry to allylic ethers (Scheme 36) [196, 197]. Excellent regioselectivity was obtained for the addition of the alcohols at the less hindered terminal carbon of the allene. Nishina and Yamamoto [198] extended the intermolecular hydrofunctionalization of allenes using $Au(PPh_3)Cl$ and AgOTf as the catalyst concluding that the axial chirality of allenes is transferred to the products with high enantioselectivities during the hydroamination, although racemization was observed in the hydroalkoxylation reaction. In addition, one year later Zang and co-workers proposed a regio- and stereoselective Au(I)-catalyzed intermolecular hydroalkoxylation of aryl– and alkoxy–allenes using PPh_3AuNO_3 catalyst [199, 200].



Scheme 34 Proposed pathways for the gold-catalyzed regiodivergent synthesis of halofurans

Scheme 35 Gold(I)-catalyzed reaction of allenyl carbinol esters





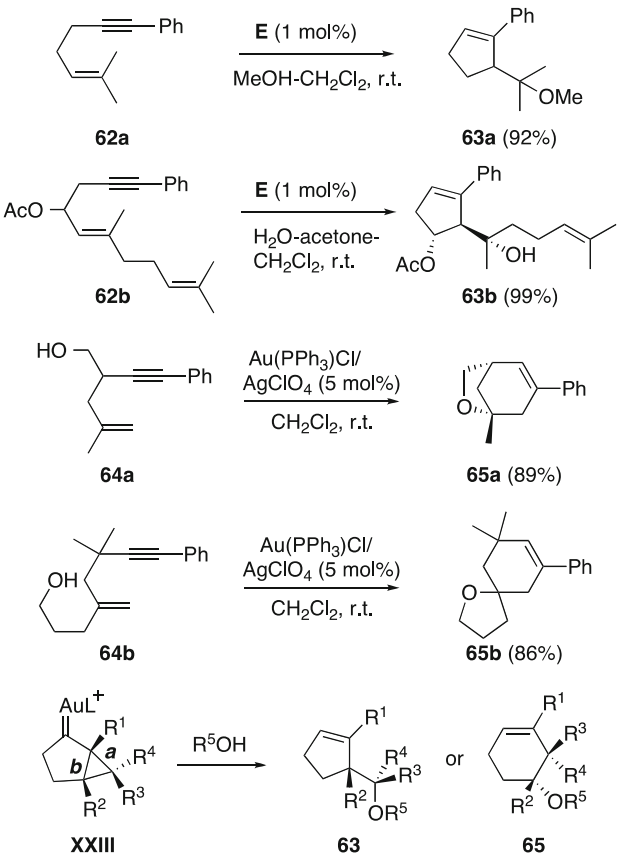
Scheme 36 Intermolecular hydroalkoxylation of allenes catalyzed by gold(I)

3 Addition of Nucleophiles to 1,*n*-Enynes

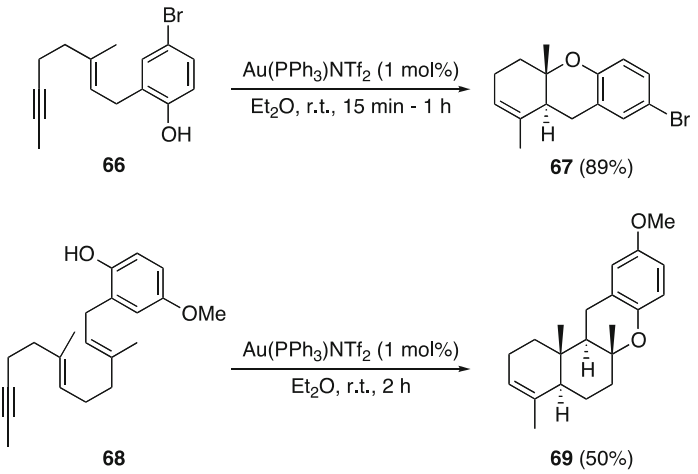
3.1 Hydroxycyclization and Alkoxycyclization of 1,5-Enynes

1,5-Enynes such as **62a**-**b** react with alcohols or water in the presence of gold(I) catalysts to give adducts **63a**-**b** (Scheme 37) [67, 76, 201–203]. Whereas products **63a**-**b** are formed by cleavage of bond ***a*** in intermediates **XXIII**, the intramolecular hydroxycyclizations of 1,5-enynes **64a**-**b** to give six-membered ring derivatives **65a**-**b** take place by cleavage of bond ***b*** in **XXIII** [204]. In a mechanistically related transformation, *N*-(hex-5-enynyl)-*tert*-butyloxycarbamates react in a formal [4 + 2] cycloaddition process with gold(I) catalysts [205]. Enenyl carbonates also undergo related gold(I)-catalyzed tandem cyclization reactions [206].

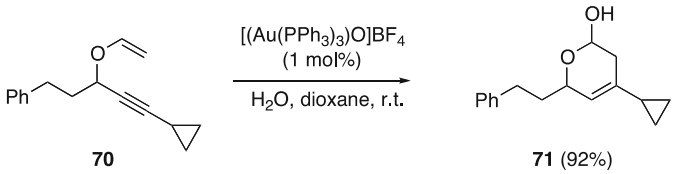
Phenols such as **66** also react intramolecularly with 1,5-enynes to give tricyclic products **67** stereospecifically (Scheme 38) [207]. The reaction was extended to a



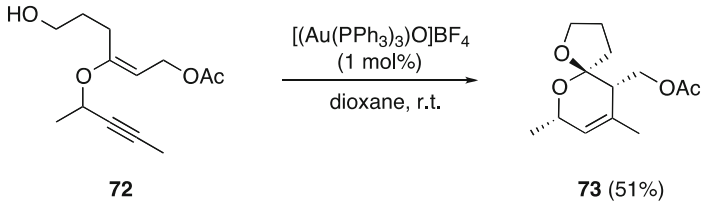
Scheme 37 Au(I)-catalyzed hydroxy- and alkoxycyclizations of 1,5-enynes



Scheme 38 Intramolecular hydroxycyclization with phenols



Scheme 39 Intermolecular reaction of propargyl vinyl ether **70** with water

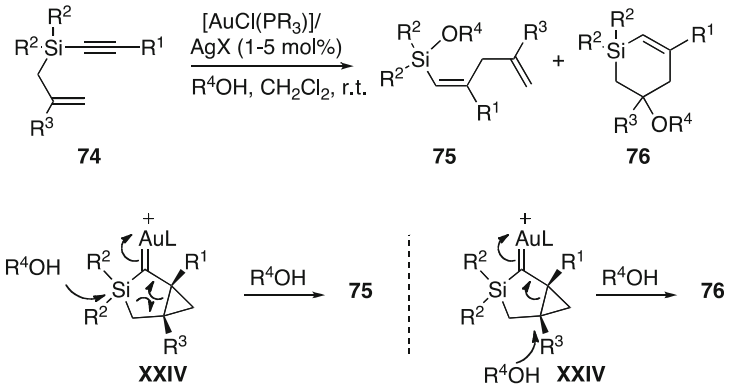


Scheme 40 Intramolecular reaction of propargyl vinyl ethers

substituted 1,5-enyne **68**, which gave tetracyclic derivative **69**. Related polycyclizations can be carried out using $Hg(OTf)_2$ as a catalyst [208].

Reaction of propargyl vinyl ethers **70** in the presence of water or alcohols leads to dihydropyrans **71** (Scheme 39) [209]. The intramolecular version of this reaction from substrates such as **72** leads to spiroketals **73** with good stereocontrol (Scheme 40) [209]. In the absence of nucleophiles, propargyl vinyl ethers undergo Claisen rearrangement with gold(I) catalysts to give allenes [55, 210–212]. Similar transformations catalyzed by gold- [49] or palladium [213] have also been reported.

Allyl silyl alkynes **74** react similarly with alcohols in the presence of gold(I) catalysts to give the alkenylsilanes **75** and/or products **76** of alkoxycyclization

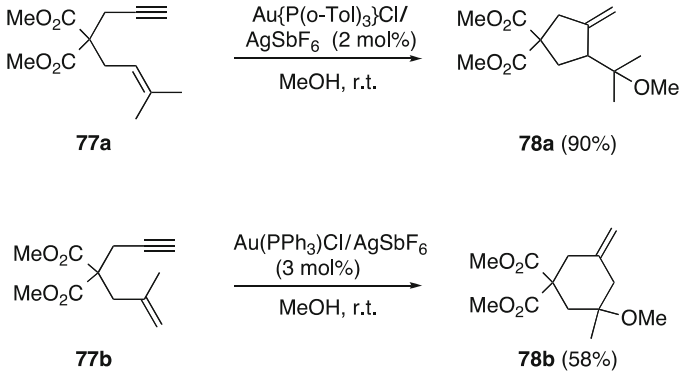


Scheme 41 Au(I)-catalyzed reaction of allyl silyl alkynes

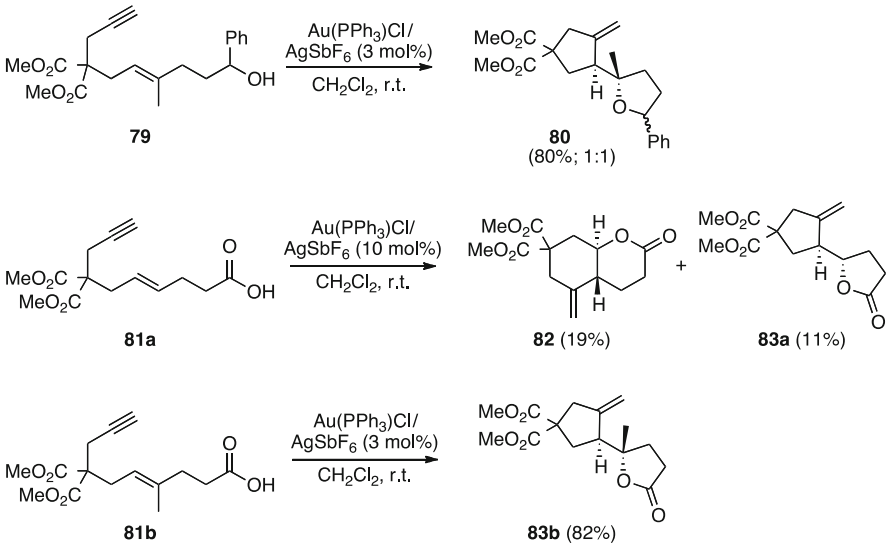
(Scheme 41) [214, 215]. These products are formed by an endocyclic attack of the initial cyclopropyl gold carbene **XXIV** followed by attack of the nucleophile at either the cyclopropane or at the silicon atom.

3.2 Hydroxycyclization and Alkoxycyclization of 1,6-Enynes

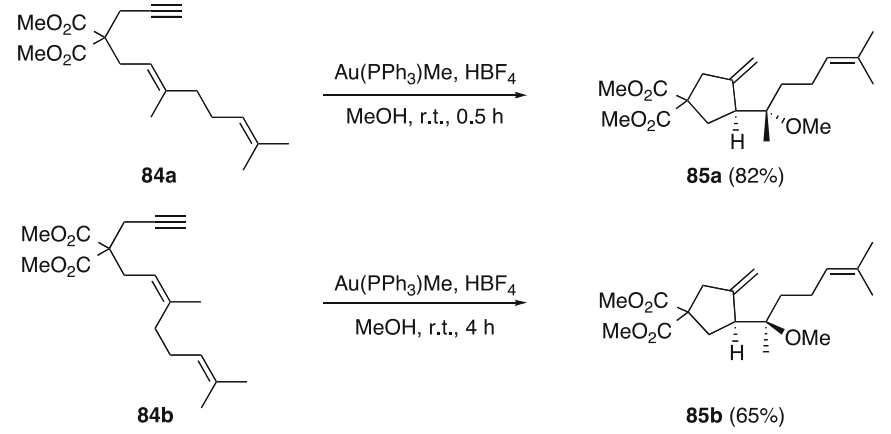
The Pt(II)-catalyzed addition of water or alcohols to 1,6-enynes is a very general reaction which can also take place, albeit less efficiently, using Pd(II) as a catalyst [216–225]. Ru(II) complexes have also been used for the hydroxycyclization of 1,6-enynes [216, 226]. 1,6-Enynes also react stereospecifically with alcohols or water in the presence of Au(I) catalysts under milder conditions than with other metal catalysts [48, 56, 76, 80, 218, 227–232]. This reaction can be performed inter- (Scheme 42) or intramolecularly (Scheme 43). In the first case, the substitution



Scheme 42 Intermolecular Au(I)-catalyzed hydroxy- and alkoxycyclizations of 1,6-enynes



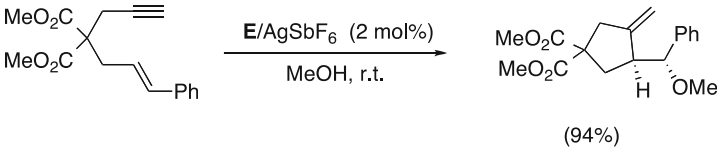
Scheme 43 Intramolecular Au(I)-catalyzed hydroxycyclization of 1,6-enyne



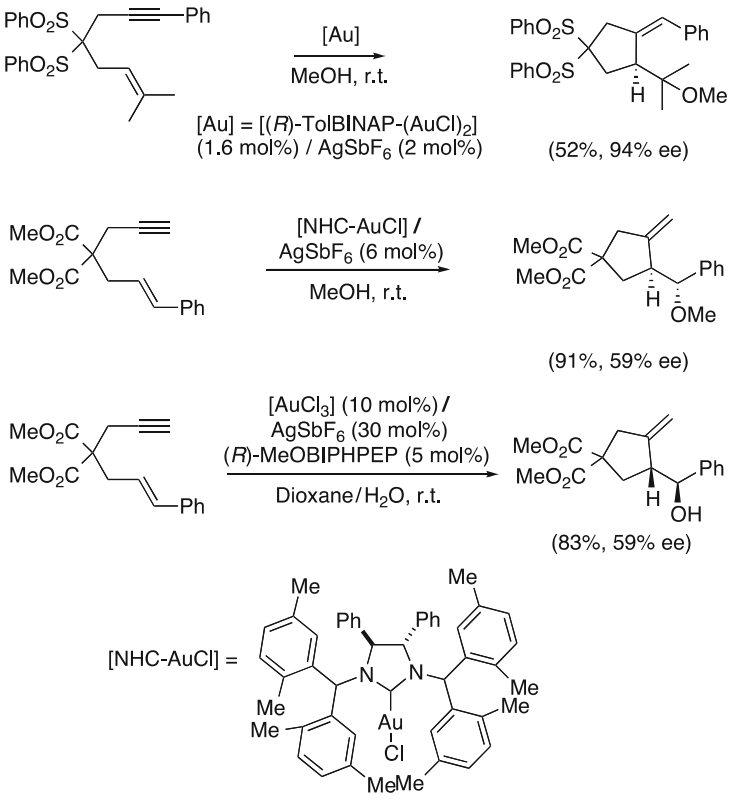
Scheme 44 Methoxycyclization of dienynes **84a-b**

pattern at the alkene usually dictates the overall regioselectivity (5-*exo-trig* in **77a** vs. 6-*endo-trig* in **77b**). In the later case, enynes bearing hydroxy groups, such as **79**, react with Au(I) to give cyclic ethers of type **80**. In a similar process, the intramolecular reaction of carboxylic acids to enynes gives rise to lactones (Scheme 43) [233]. These cyclizations exhibit the characteristics associated with cationic polyene cyclization reactions.

Although similar results were obtained from catalysts generated in situ from [AuMe(PPh_3)] and a protic acid (Scheme 44) [59] or [AuCl(PPh_3)] and $AgSbF_6$, in



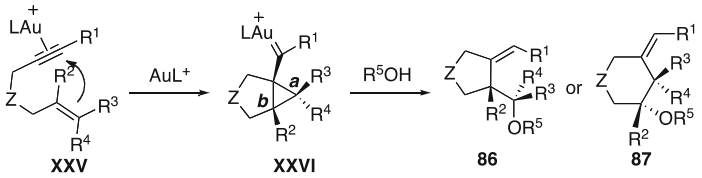
Scheme 45 Au(I)-catalyzed hydroxycyclization with bulky phosphines and NHC ligands



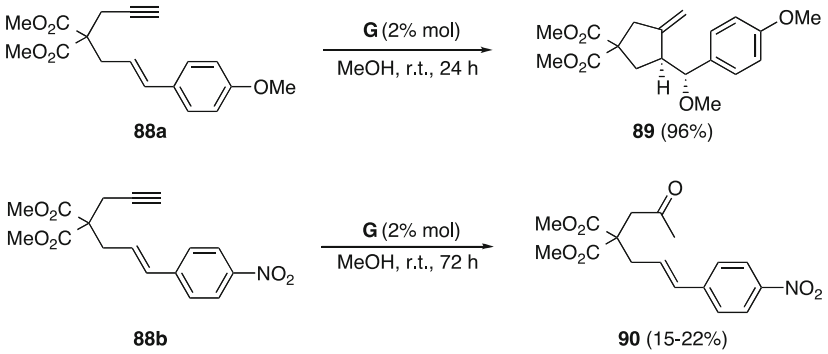
Scheme 46 Asymmetric gold(I)-catalyzed hydroxycyclization of 1,6-enynes

the stereospecific transformation of **84a** and **84b** into **85a** and **85b**, respectively, the catalysts of choice for the hydroxy- and alkoxycyclizations of 1,6-enynes are those bearing bulky biphenyl phosphines (Scheme 45) [63, 227, 234]. Similar results can be obtained with NHC–Au(I) [89] or Au(III) complexes as catalysts [76, 80, 229, 235].

Asymmetric methoxycyclization of 1,6-enynes takes place selectively with gold (I) complexes bearing chiral bidentate phosphines and *N*-heterocyclic carbenes leading to good levels of enantioselectivity (Scheme 46) [201, 230, 232, 236].



Scheme 47 General mechanism for the gold(I)-catalyzed hydroxy- and alkoxycyclization of 1,6-enynes



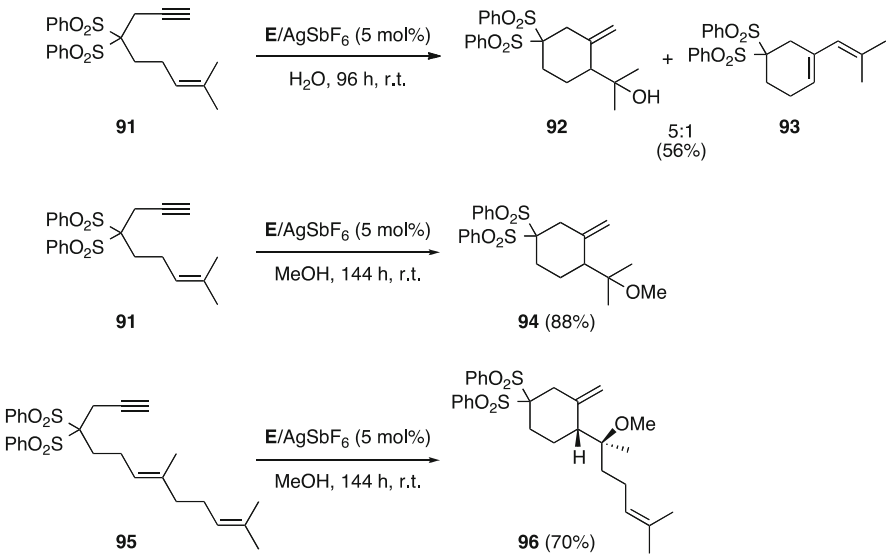
Scheme 48 Hydration of 1,6-enyne catalyzed by gold(I)

Mechanistically, formation of products of *exo*-trig and *endo*-trig cyclization can be explained by the attack of the nucleophiles to cyclopropyl gold(I) carbene intermediates **XXVI** at carbons ***a*** or ***b*** to form products **86** or **87** (Scheme 47), similarly to that found for Pt(II) ([235], an example of gold-catalyzed methoxycyclization of an allenene [237]). In the first step, the alkene reacts with the alkyne–gold(I) complex in an electrophilic addition process.

Usually, the hydroxycyclization is much faster than the direct nucleophilic addition of water to the alkyne to form the corresponding methyl ketone. However, hydration of the alkyne takes place with 1,6-enynes in which the alkene bears electron withdrawing substituents that reduce its reactivity in the electrophilic addition [227]. Thus, enyne **88a** reacts with MeOH in the presence of gold(I)-catalyst to give **89** in excellent yield, whereas **88b** with a *p*-nitrophenyl group at the terminal carbon of the alkene gives ketone **90** (Scheme 48). Formation of ketone **90** is the result of addition of water contained in the solvent, since addition of 4 Å molecular sieves inhibits the hydration reaction [50, 51].

3.3 Hydroxycyclization and Alkoxycyclization of 1,7-Enynes

The cycloisomerizations of 1,7-enynes have been less studied. Chatai and Murai reported the first example of a skeletal rearrangement of a 1,7-enyne using [RuCl



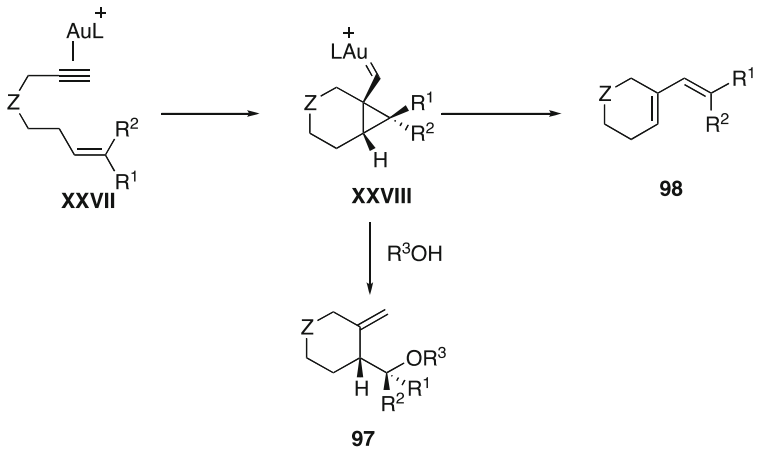
Scheme 49 Hydroxy- and methoxycyclization of 1,7-enynes

$(CO)_2]_2$ as a catalyst [238]. Similar results have been obtained using $PtCl_2$ [239, 240], $PtCl_4$ [241], $[IrCl(CO)_3]_n$ [242], $GaCl_3$ [243–245], and $InCl_3$ [246]. With the exception of rearrangements catalyzed by $GaCl_3$, which can proceed with 10–20 mol% catalyst at 23–40°C, all other metals catalyzed the process at higher temperatures (80–110°C) [247].

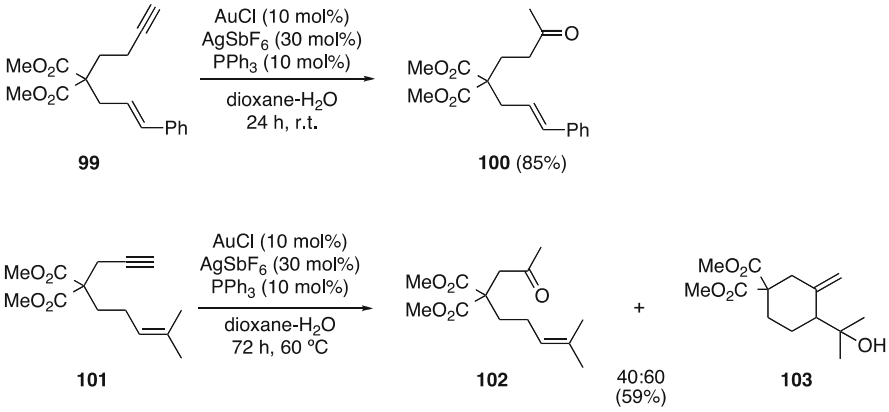
A few examples of skeletal rearrangement and hydroxylation of 1,7-enynes were reported using Au(I) [248] and Hg(II) [249] as catalysts, respectively. The hydroxy- and alkoxycyclizations of 1,7-enynes take place similarly to 1,6-enynes with a variety of gold(I) catalysts [250]. Better results were obtained in these cases with gold(I) complexes bearing bulky biphenylphosphines [57, 251]. The reaction of 1,7-enyne **91** in aqueous acetone afforded mixtures of alcohol **92** and rearranged diene **93**, whereas the reaction in methanol led exclusively to the product of methoxycyclization **94** (Scheme 49). The gold(I)-catalyzed methoxycyclization of **95** gave stereospecifically **96** in 70% yield.

These results are consistent with reaction of 1,7-enynes by selective activation of the alkyne by Au(I) in complexes **XXVII** leading to cyclopropyl gold(I)-carbenes **XXVIII**, which react with water or alcohols to form stereospecifically adducts **97**. Alternatively, intermediates **XXVIII** can undergo single-cleavage rearrangement to give dienes **98** (Scheme 50).

The hydroxycyclization reaction of homopropargylic enyne **99** did not proceed as previously reported for 1,6-enynes and suffered the addition of water to the alkyne moiety (alkyne hydration) to give ketone **100** (Scheme 51) (Sect. 2.1, 3.2) [229]. 1,7-Enyne **101** did not react at room temperature, although ketone **102** and six-membered ring alcohol **103** could be obtained when the reaction was carried out at 60°C.



Scheme 50 Mechanism of gold-catalyzed cyclization of 1,7-enynes



Scheme 51 Hydroxycyclization of homopropargylic and homoallylic substituted 1,7-enynes

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Transition-Metal-Catalyzed S–H and Se–H Bonds Addition to Unsaturated Molecules

Akiya Ogawa

Abstract This chapter deals with the transition-metal-catalyzed hydrothiolation and hydroselenation of alkynes and allenes and related unsaturated compounds with thiols and selenols. In these reactions, the regio- and/or stereoselectivities of the addition products can be controlled by switching the transition metal catalysts. Metal sulfides and selenides (RE-ML_n, E = S, Se, M = Ni, Pd, Rh, Zr, Sm, etc.) play an important role as key catalyst species in these hydrothiolation and hydroselenation. The introduction of carbon monoxide into these hydrothiolation and hydroselenation systems leads to novel carbonylation with simultaneous addition of thio and seleno groups to unsaturated bonds.

Keywords Carbonylation · Hydroselenation · Hydrothiolation · Transition metal catalysts · Vinyl sulfides

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
An	Actinide
Ar	Aryl
t-Bu	*tert*-butyl
cat	Catalyst
c-Hex	Cyclohexyl
coe	Cyclooctene
cod	1,5-cyclooctadiene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
DIOP	*O*-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
dppp	1,3-bis(diphenylphosphino)propane
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBM-segphos	5,5'-bis{di(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino}-4,4'-bi-1,3-benzodioxole
equiv	Equivalent
GPC	Gel permeation chromatography
i-Pr	Isopropyl
IMes	*N*,*N*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
Ln	Lanthanide
ML_n	Transition metal complex (M: metal L: ligand)
mol	Mole(s)
Me	Methyl
Ms	Methanesulfonyl (mesyl)
NHC	*N*-heterocyclic carbene ligands
Ph	Phenyl
py	Pyridine
R	Organyl substituent
rt	Room temperature
SEM	Scanning electron microscopy
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tp*	Hydrotris(3,5-dimethylpyrazolyl)borate
p-TsOH	*p*-toluenesulfonic acid

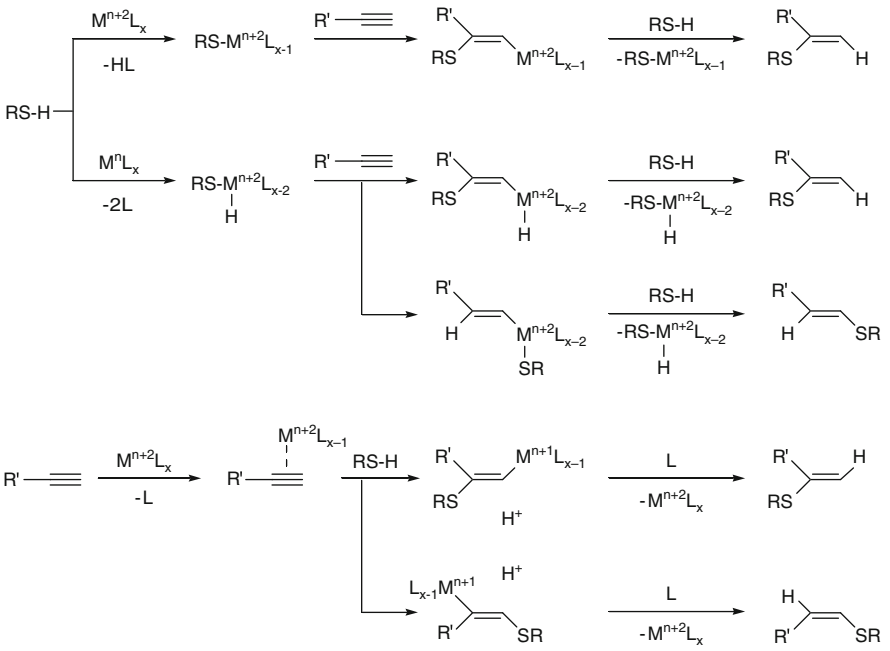
1 Introduction

Transition-metal-catalyzed addition reactions of heteroatom compounds bearing a heteroatom–hydrogen linkage to carbon–carbon unsaturated bonds are very useful in terms of highly regio- and stereoselective synthesis of heteroatom compounds with excellent atom economy. Indeed, transition-metal-catalyzed hydroboration, hydrosilylation, and hydrostannation are widely employed for organic synthesis. In contrast, the transition-metal-catalyzed addition of group 16 heteroatom compounds bearing a sulfur–hydrogen or selenium–hydrogen linkage to unsaturated compounds has remained largely undeveloped. This might be partly due to the widespread prejudice that organic sulfur and selenium compounds often bind strongly to the catalysts, thus poisoning them and making the catalytic reactions ineffective [1]. During the last two decades, however, examples of efficient, highly selective addition of thiols and selenols to carbon–carbon unsaturated bonds in the presence of transition metal catalysts have been reported. This chapter deals with the highly selective transition-metal-catalyzed hydrothiolation and hydroselenation of alkynes and related carbon–carbon unsaturated compounds using thiols and selenols [2–20].

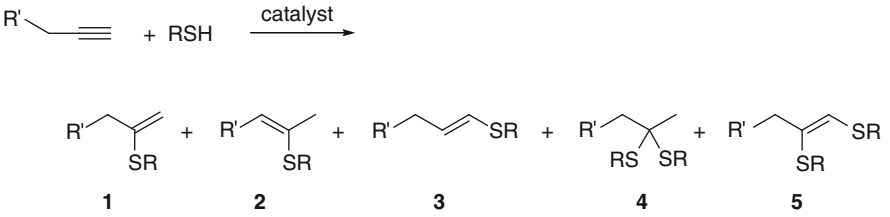
2 Transition-Metal-Catalyzed Hydrothiolation with Thiols

Thiols have been widely employed as the sources of ligands for various transition metals. In the stoichiometric reactions of thiols with transition metal complexes, two types of processes are generally operative (Scheme 1).

One is the ligand-exchange reaction between high-valent transition metal complexes ($M^{n+2}L_x$) and thiols to give the complexes bearing only thiolate ligands (RS-$M^{n+2}L_{x-1}$). The other is the oxidative addition of thiols to low-valent transition metals (M^nL_n) to give the corresponding transition metal complexes bearing both hydride and thiolate ligands (RS-$M^{n+2}L_{x-2}$-H). The reaction of the former complexes (RS-$M^{n+2}L_{x-1}$) with carbon–carbon unsaturated compounds such as alkynes may proceed via thiometallation, in which relatively more bulky $M^{n+2}L_{x-1}$ is bonded at the terminal carbon of alkynes. On the other hand, in the reaction of the latter complexes (RS-$M^{n+2}L_{x-2}$-H) with alkynes both hydrometallation and thiometallation processes are possible. These processes proceed via *syn*-addition. Alternative pathway for the addition of thiols to alkynes involves coordination of alkynes to transition metals and then nucleophilic addition of thiols (or thiolate anions) to the alkynes. These processes take place via *anti*-addition. By controlling these pathways, regio- and stereoselective hydrothiolation of alkynes is expected to be attained successfully.



Scheme 1 Mechanistic pathways for hydrothiolation of alkynes



Scheme 2 Product selectivity in hydrothiolation of terminal alkynes

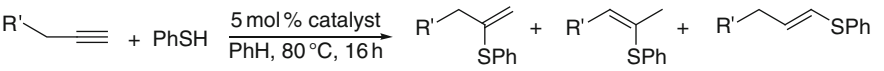
2.1 Hydrothiolation of Alkynes

In the transition-metal-catalyzed addition reactions of thiols to terminal alkynes, several addition products, i.e., Markovnikov-type adduct **1**, Markovnikov addition and then double-bond-isomerization product **2**, *anti*-Markovnikov adduct **3**, double hydrothiolation product **4**, and bisthiolation product **5**, may be formed (Scheme 2). Controlling the product selectivity can be attained by the selection of transition metal complexes as catalysts, the use of additives, and/or the optimization of the reaction conditions (solvent, temperature, molar ratios of the starting materials, and so on).

2.1.1 Markovnikov Addition

Palladium Catalysts

The reaction of benzenethiol with 1-octyne in the presence of various transition metal complexes is conducted as a model reaction, and a number of transition metal complexes are found to catalyze the hydrothiolation of 1-octyne (Scheme 3) [21]. Among the catalysts examined, palladium diacetate ($Pd(OAc)_2$) exhibits an excellent catalytic activity toward the Markovnikov addition of PhSH to 1-octyne, and 2-phenysulfurnyl-1-octene (**1a**) is obtained regioselectively. Bis(benzonitrile)palladium dichloride ($PdCl_2(PhCN)_2$) can form cationic palladium species more easily compared with $Pd(OAc)_2$. The use of $PdCl_2(PhCN)_2$ as a catalyst causes Markovnikov addition of PhSH to 1-octyne and the following double-bond-isomerization reaction, which afford 2-phenylsulfanyl-2-octene (**2a**) as the major product. Similar product selectivity is also observed when tetrakis(triphenylphosphine)platinum ($Pt(PPh_3)_4$) is employed as the catalyst. It is known that the stoichiometric reaction of $Pt(PPh_3)_4$ with thiol forms $PhS\text{-}PdH(PPh_3)_2$ via oxidative addition [22, 23]. The platinum species can contribute to the addition of thiols to alkynes [24, 25] and the double-bond-isomerization to give the hydrothiolation product **2a**. In the case of tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) catalyst, 1,2-bis(phenylsulfanyl)-1-octene (**5a**) is obtained beside **2a**. Oxidative addition of PhSH to the low-valent palladium complex may lead to the formation of $PhS\text{-}PdH(PPh_3)_2$. The palladium hydride species having phosphines as the ligands is reactive to generate in situ $Pd(SPh)_2(PPh_3)_2$, resulting in the formation of several addition products. In general, platinum hydride species are more stable than the corresponding palladium hydride species, and therefore the $Pt(PPh_3)_4$-catalyzed hydrothiolation of 1-octyne indicates excellent product selectivity compared with the $Pd(PPh_3)_4$-catalyzed reaction.



2 M 1 equiv (R ' = *n*-C_5H_{11}) **1a** **2a** **3a**

	1a	**2a**	**3a**
$Pd(OAc)_2$ (THF, 40 °C)	85%	<1%	<1%
$Pd(OAc)_2$	67%	2%	<1%
$Pd(PPh_3)_4$	1%	45%	4%
$PdCl_2(PhCN)_2$	2%	73%	0%
$Pt(PPh_3)_4$	2%	80%	18%
$NiCl_2(PPh_3)_2$	1%	22%	2%
$RhCl(PPh_3)_3$	14%	23%	52% [98/2][a]
none (20 h)	0%	0%	65% [48/52][a]

[a] *E*/*Z* ratio.

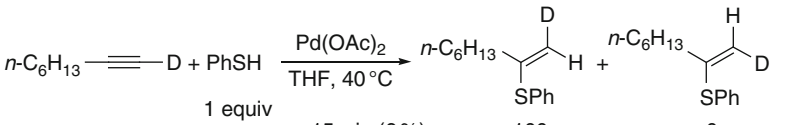
Scheme 3 Hydrothiolation of 1-octyne catalyzed by transition metal complexes

Even in the absence of catalyst, thiols add to alkynes under neutral conditions to afford *anti*-Markovnikov-type vinylic sulfides with excellent regioselectivity usually as a stereoisomeric mixture. Indeed, the reaction of benzenethiol with 1-octyne in the absence of transition metal catalyst provides *anti*-Markovnikov adduct **4a** regioselectively with the *E*:*Z* ratio of ca. 1:1. This hydrothiolation takes place, most probably via the radical process induced by trace amounts of oxygen existed in the reaction system. The radical addition of thiols to alkynes sometimes seems to proceed even in the presence of transition metal catalysts. Accordingly, when the *anti*-Markovnikov adducts are obtained with approximately equal amounts of *E*- and *Z*-isomers, the following possibility is present: the *anti*-Markovnikov adducts are formed by the radical process, regardless of the presence of transition metal catalysts.

The $Pd(OAc)_2$-catalyzed hydrothiolation with thiols can be applied to a variety of terminal alkynes and Markovnikov-type addition products **1** are obtained regioselectively in good yields. Functionalities such as hydroxy, amino, ester, and alkenyl groups are tolerant toward the regioselective hydrothiolation. The hydrothiolation also proceeds smoothly with internal alkynes to give a stereoisomeric mixture of vinyl sulfides, although the *E*-isomer is predominantly formed at the beginning of the reaction. Interestingly, the addition to 2-octynoic acid affords 3-(phenylsurfanyl)-2-octenoic acid with high regio- and stereoselectivity (87%, $E/Z = 98/2$; its regioisomer (2%)). This excellent regioselectivity may be attained by the coordination of carboxylic group to the palladium.

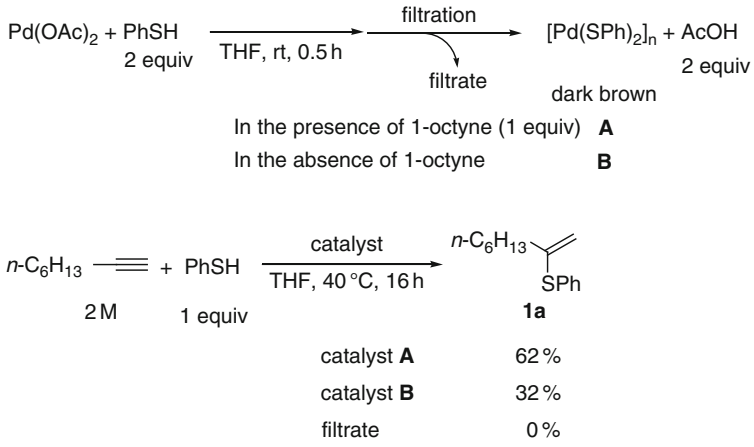
To ascertain the stereochemistry of this $Pd(OAc)_2$-catalyzed hydrothiolation of terminal alkynes, the reaction of PhSH with 1-octyne-1-*d* (containing 93% *d*) is monitored by ^{1}H NMR spectroscopy. The *E*:*Z* ratio of the thiolation products is 100:0 at the initial stage, and then *E*-isomer as the kinetic product gradually isomerized to *Z*-isomer. These results clearly indicate that the hydrothiolation proceeds via *syn*-addition at least at the initial stage (Scheme 4).

To get insight into the reaction pathway for the $Pd(OAc)_2$-catalyzed hydrothiolation, several mechanistic investigations are examined. At first, the reaction of $Pd(OAc)_2$ with two equivalents of PhSH in THF in the presence or



15 min (6 %)	100	0
2 h (40 %)	96	4
4 h (59 %)	89	11
8 h (81 %)	86	14
17 h (94 %)	67	33
		(d_1 94 %, d_2 0 %)

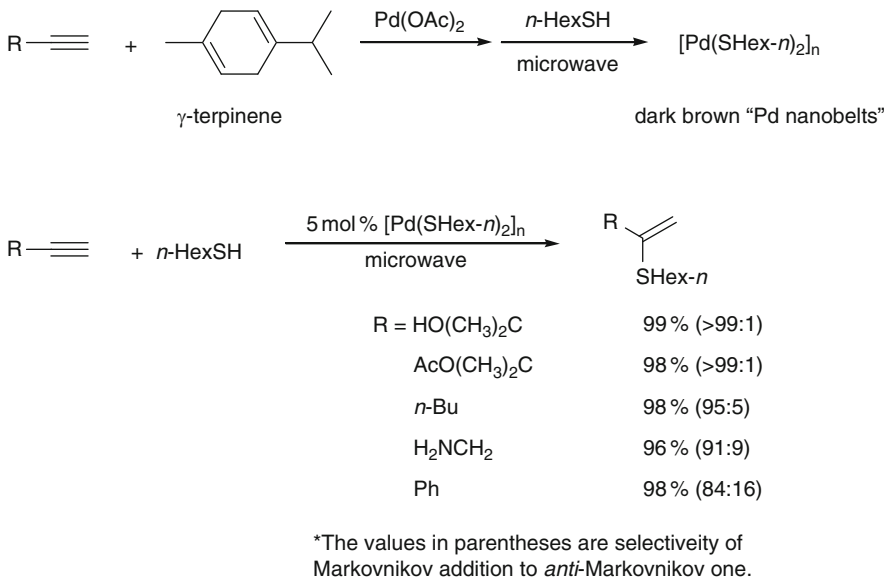
Scheme 4 *Syn*-addition of PhSH to 1-octyne-1-*d*



Scheme 5 Catalytic activity of palladium sulfide for hydrothiolation

absence of 1-octyne is attempted. In both cases (in the presence or absence of 1-octyne), dark brown precipitates **A** or **B** are formed immediately with the formation of two equivalents of AcOH (Scheme 5) [2, 7]. The elemental analysis of these dark brown precipitates **A** or **B** suggests the formation of $[Pd(SPh)_2]_n$ from the ligand-exchange reaction of $Pd(OAc)_2$ with two equivalents of PhSH. The catalytic hydrothiolation of 1-octyne with PhSH proceeds well in the presence of the dark brown precipitate **A** (prepared in the presence of 1-octyne), whereas the dark brown precipitate **B** (prepared in the absence of 1-octyne) is less effective for the catalytic hydrothiolation. On the other hand, no hydrothiolation of 1-octyne takes place by using the filtrate instead of the dark brown precipitates. These results strongly suggest that the dark brown precipitate, i.e., $[Pd(SPh)_2]_n$, is the real catalyst species and this $Pd(OAc)_2$-catalyzed hydrothiolation has the nature of heterogeneous catalysis.

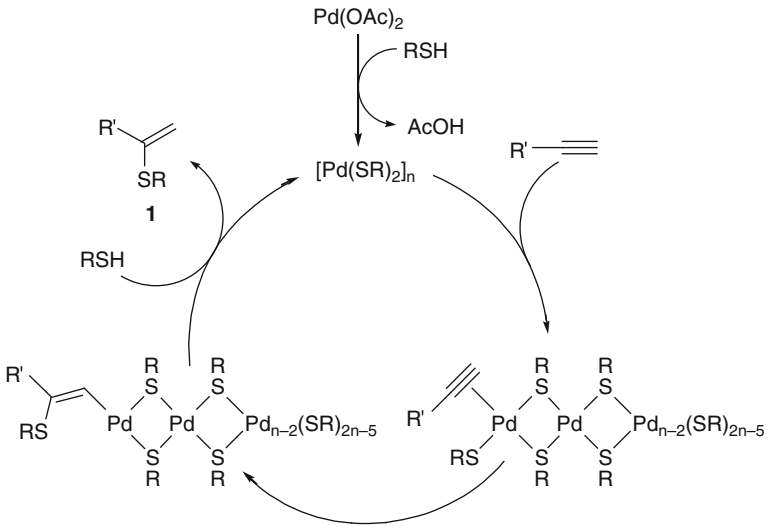
The key species, $[Pd(SPh)_2]_n$, is considered to have a polymeric structure bearing both terminal and bridged sulfide groups, and is insoluble in most of organic solvents. The hydrothiolation may take place on the surface of the precipitated $[Pd(SPh)_2]_n$. Owing to the insolubility of the $[Pd(SPh)_2]_n$ in organic solvents, the determination of the molecular weight of $[Pd(SPh)_2]_n$ by gel permeation chromatography (GPC) is difficult. However, the palladium sulfide **B** prepared by the reaction in the absence of 1-octyne might be much more polymeric than the palladium sulfide **A** prepared by the reaction in the presence of 1-octyne, because the polymerization by the sulfur bridging may be retarded by the coordination of 1-octyne to the palladium. Monodentate terminal sulfanyl groups are active for the desired hydrothiolation. Most probably, bidentate bridged sulfanyl groups are inactive (or less active) for the hydrothiolation, and conceivably the polymerized palladium sulfide with large molecular weight is considered as "catalyst poisoning." To avoid the poisoning, therefore, it is important technically to mix the palladium catalyst and alkynes before addition of thiols (The order of addition is usually as follows: the catalyst, solvent, alkyne, then thiol).



Scheme 6 Synthesis of Pd nanobelts and their catalytic activity

The structures of the palladium sulfides have been confirmed clearly by scanning electron microscopy (SEM) study [26]. When $Pd(OAc)_2$ dissolved in alkyne in the presence of γ-terpinene is allowed to react with cyclohexanethiol upon microwave heating, nanostructured Pd species (Pd nanobelts) is formed in 85% yield. γ-Terpinene acts as an excellent radical trapper and suppresses the formation of *anti*-Markovnikov addition product **3** by radical pathway. On the other hand, the addition of thiols to $Pd(OAc)_2$ followed by addition of alkyne leads to amorphous particles in the μm-size region. The formed Pd nanobelts exhibits excellent catalytic activity toward the hydrothiolation of alkynes. In particular, the hydrothiolation with alkanethiols proceeds efficiently with excellent regioselectivity upon microwave heating (Scheme 6).

A possible pathway for the $Pd(OAc)_2$-catalyzed hydrothiolation is shown in Scheme 7. The ligand-exchange reaction between $Pd(OAc)_2$ and PhSH leads to $Pd(SPh)_2$, which reacts each other to form the polymeric palladium sulfide species. Alkyne coordinates to the terminal palladium of the polymeric palladium sulfides and then the alkyne inserts into the monodentate sulfanyl-Pd bond. Since polymeric palladium site is bulky, the sulfanylpalladation occurs with bonding of the Pd site to the terminal carbon of alkyne regioselectively to generate vinylpalladium species. Protonation of the vinylpalladium species with PhSH affords the hydrothiolation product **1** with regeneration of the catalyst. In the cases of arenethiols, the protonation process proceeds smoothly, due to the higher acidity of arenethiols compared with alkanethiols ($pK_a = 6.5$ (PhSH); 10.66 (*n*-alkaneSH)). In the cases of alkenethiols, direct protonation is somewhat difficult to take place due to the lower acidity of them. Therefore, the σ-bond metathesis between vinylic C–Pd



Scheme 7 A possible catalytic cycle for the $Pd(OAc)_2$-catalyzed hydrothiolation

and RS–H via the four-centered (vinylic C, Pd, S, and H) transition state is an alternative pathway.

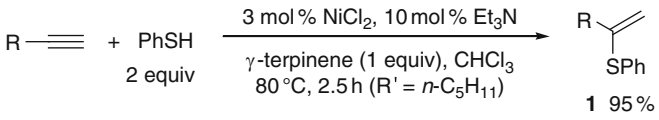
Some additional comments about the mechanism are as follows: It is important to discuss the difference in the coordination ability between alkylsulfanyl and arylsulfanyl groups. In general, alkyl group is among electron-donating groups, whereas the aryl group on sulfur conjugates with the lone-pair on the sulfur of ArS group. This conjugation decreases the coordination ability of ArS group. Since alkylsulfanyl group has the higher coordination ability, alkylsulfanyl group acts as bidentate ligands to bridge between two palladiums [27].

Another mechanistic aspect is the reductive elimination from the vinylpalladium intermediate, which may afford the vicinal disulfanylalkene **5**. In the presence of phosphines as ligands, the reductive elimination is relatively fast. Since no phosphine is employed for this $Pd(OAc)_2$-catalyzed hydrothiolation, the reductive elimination to give **5** does not proceed smoothly.

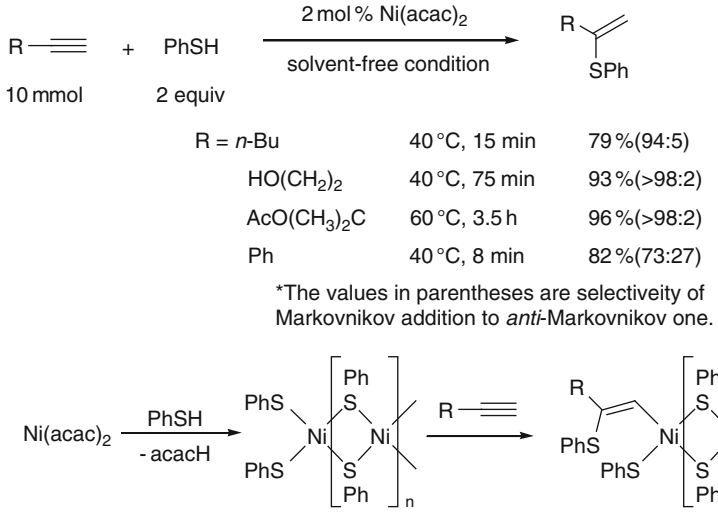
Nickel Catalysts

Markovnikov-type addition of benzenethiols to alkynes has been investigated in detail by using nickel catalysts such as nickel dichloride ($NiCl_2$) [28]. The $NiCl_2$-catalyzed hydrothiolation of alkynes with PhSH has been attained by using γ-terpinene and triethylamine as additives (Scheme 8).

γ-Terpinene as a radical trapper inhibits the *anti*-Markovnikov addition by radical mechanism. Triethylamine contributes to the increase in the yield and selectivity of Markovnikov-type addition product by activation of $NiCl_2$.



Scheme 8 $NiCl_2$-catalyzed hydrothiolation of 1-heptyne



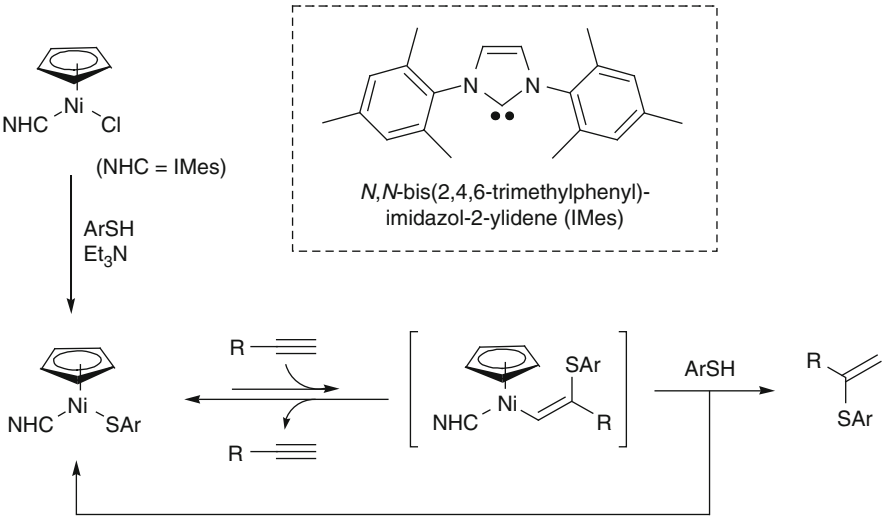
Scheme 9 $Ni(acac)_2$-catalyzed hydrothiolation of alkynes

Furthermore, excluding phosphine and phosphite from the catalytic system inhibits the formation of the vicinal disulfanylalkene **5**.

An excellent nickel-based nanosized catalytic system has been developed for the practical synthesis of vinylic sulfides **1** (Scheme 9) [29, 30].

Inexpensive and easily available nickel acetylacetonate ($Ni(acac)_2$) is employed as the catalyst precursor. The procedure can be easily scaled-up to prepare up to 50 g of the vinyl sulfides with high regioselectivity. Moreover, solvent-free conditions without chromatographical purification attain eco-friendly synthetic method of vinyl sulfides. The mechanistic study indicates that the catalytic hydrothiolation takes place under heterogeneous conditions with alkyne insertion into the Ni–S bond of nanosized nickel sulfide species.

A novel homogeneous catalytic system using nickel complexes bearing *N*-heterocyclic carbene ligands (NHC) has been also developed for the regioselective hydrothiolation of alkynes (Scheme 10) [31–33]. For example, *N*,*N*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) is used as a representative NHC, and the formed CpNi(IMes)Cl indicates an excellent catalytic activity toward the Markovnikov-type addition of thiols to alkynes, which proceeds efficiently with high regioselectivity (61–87% yields; up to 31:1 selectivity). The stabilization of highly reactive metal complexes by the greater σ-donation of NHC makes it



Scheme 10 Homogeneous hydrothiolation of alkynes catalyzed by CpNi(NHC)Cl

possible to gain insight into the mechanism for this hydrothiolation under homogeneous conditions.

In the presence of Et_3N, CpNi(NHC)Cl reacts with arenethiols to form the corresponding nickel sulfides (CpNi(NHC)(SAr)) quantitatively. Furthermore, the structure of CpNi(NHC)(SAr) is confirmed by X-ray analysis. A catalytic activity of the CpNi(NHC)(SAr) for the regioselective hydrothiolation is demonstrated. When the hydrothiolation of 1-heptyne with PhSH is conducted in the presence of 3 mol% of CpNi(NHC)(SAr) at 60 °C for 6 h, 2-phenylsulfanyl-1-heptene is obtained in 67% yield with 8:1 selectivity (Markovnikov: *anti*-Markovnikov). While the stoichiometric reaction of CpNi(NHC)(SAr) with alkynes does not proceed in the absence of thiols even upon heating at 80 °C, the presence of thiols (2 equiv) upon heating at 70 °C for 4 h leads to 96% of the Markovnikov-type adduct along with CpNi(NHC)(SAr) (1 equiv) and thiols (1 equiv). The appearance of vinylnickel intermediate via thionickelation is not observed by NMR measurements. However, these results suggest the vinylnickel intermediate is in equilibrium with CpNi(NHC)(SAr) and alkynes. The addition of another equivalent of thiol enables the trapping of the vinylnickel intermediate, giving the vinyl sulfides.

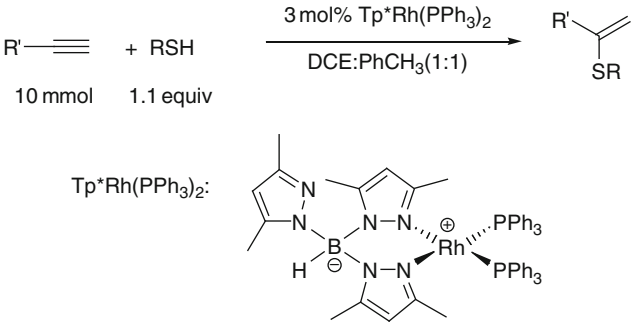
Another example of nickel-catalyzed hydrothiolation of alkynes is reported. Ni$(PPh_2Me)_4$ in the presence of $Ph_2P(O)OH$ works as a useful catalyst for the Markovnikov-type addition of 1-octyne [34]

Rhodium Catalysts

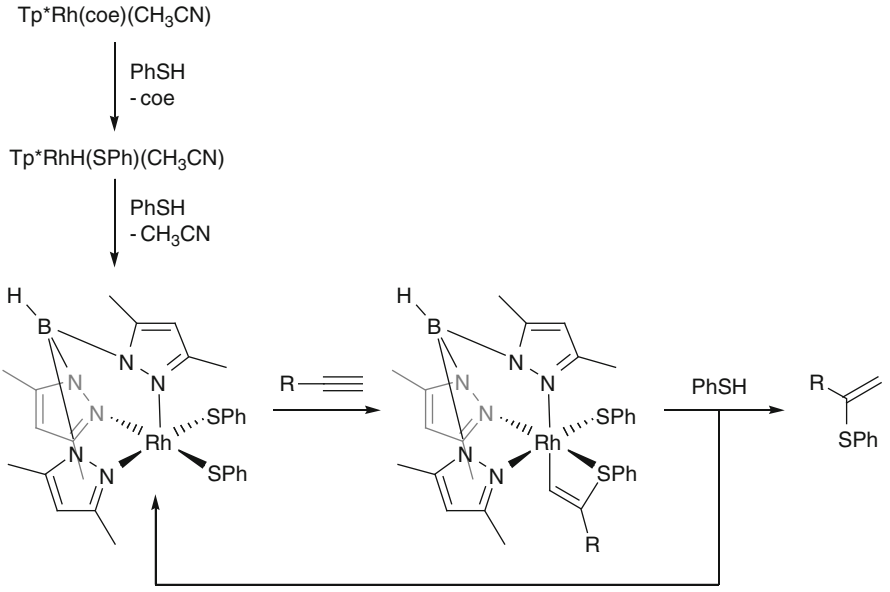
Hydrotris(pyrazolyl)borates are widely used as ligands for transition metals, and especially, rhodium pyrazolylborates have been extensively studied for stoichiometric

C–H activation reactions [35]. Rhodium pyrazolylborates, as highly electron-rich metal complexes, are found to be useful catalysts for the Markovnikov-type addition of thiols to alkynes. In particular, Tp*Rh(PPh_3)$_2$ (Tp* = hydrotris (3,5-dimethylpyrazolyl)borate) exhibits an excellent catalytic activity toward the regioselective hydrothiolation of a range of alkynes with both arene- and alkanethiols (Scheme 11) [36–40]. A variety of functional groups are well tolerated, and both sterically encumbered alkynes and thiols are successful in hydrothiolation. Electron-rich alkynes react more rapidly than electron-deficient alkynes.

Hydrothiolation of terminal alkynes is investigated by using Tp*Rh(SPh)$_2$ as the catalyst [41]. This hydrothiolation also affords Markovnikov-type addition products as the major product. Mechanistic aspects are shown in Scheme 12.



Scheme 11 Tp*Rh(PPh_3)$_2$-catalyzed hydrothiolation of alkynes

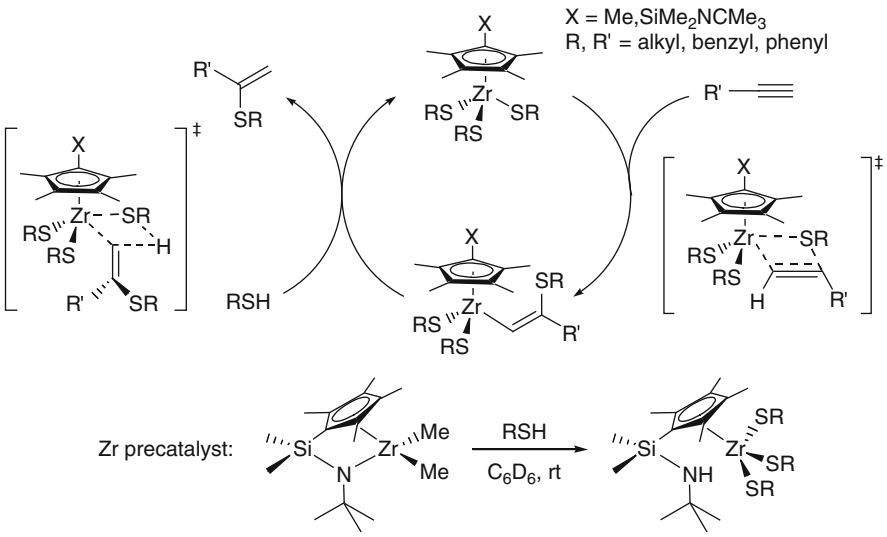


Scheme 12 Tp*Rh(SPh)$_2$-catalyzed hydrothiolation of alkynes

The reaction of Tp*Rh(coe)(CH_3CN) with 1 equiv of PhSH generates the corresponding hydrorhodium sulfide complex, Tp*RhH(SPh)(CH_3CN), via oxidative addition. Tp*RhH(SPh)(CH_3CN) does not react with alkynes. Treatment of Tp*RhH(SPh)(CH_3CN) with excess PhSH affords Tp*Rh$(SPh)_2$ to with concomitant formation of H_2. The insertion process of alkyne into the Rh–S bond takes place smoothly by the orientation that "R" group of alkyne is located at the less hindered sulfanyl site. The elimination process of the hydrothiolation product from the vinylrhodium intermediate is relatively slow, and Tp*Rh$(SPh)_2$ catalyst is re-formed.

Early Transition Metal Catalysts

Several early transition metal complexes catalyze the regioselective hydrothiolation of alkynes [42–47]. For example, the monomeric organozirconium complexes-catalyzed hydrothiolation of alkynes is shown to be highly Markovnikov selective, with selectivities up to 99%, and typically in greater than 90% yields (Scheme 13) [43]. Kinetic investigations show that the Zr precatalyst-mediated reaction between 1-pentanethiol and 1-hexyne is first order in catalyst concentration, first order in alkyne, and also first order in thiol at lower concentrations but transitions to zero order at concentrations >0.3 M. Deuterium labeling of the alkyne yields $k_H/k_D = 1.3$ (0.1), along with evidence of thiol-mediated protonolytic detachment of product from the Zr center. Based on kinetic data, this hydrothiolation is proposed to proceed through an alkyne insertion thiol protonolysis sequence with turnover-limiting alkyne insertion.

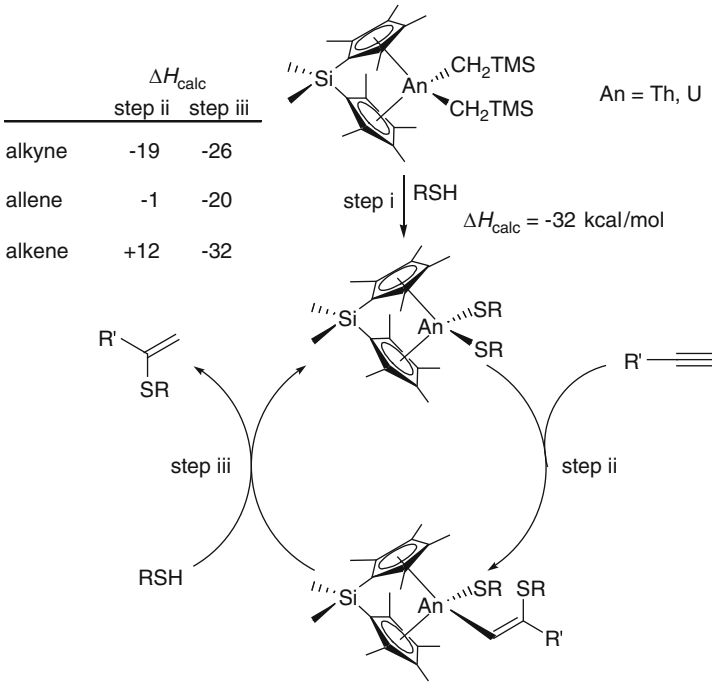


Scheme 13 Organozirconium complexes-catalyzed hydrothiolation of alkynes

The Markovnikov-selective lanthanide-mediated hydrothiolation of terminal alkynes with aliphatic, benzylic, and aromatic thiols also proceeds by using $Cp^*_2LnCH(TMS)_2$ ($Cp^* = C_5Me_5$; Ln = La, Sm, Lu) and $Ln[N(TMS)_2]_3$ (Ln = La, Nd, Y) as precatalysts [44, 45].

Kinetic investigations of the $Cp^*_2SmCH(TMS)_2$-mediated reaction between 1-pentanethiol and 1-hexyne are found to be first order in catalyst concentration, first order in alkyne, and zero order in thiol concentration. Deuterium labeling of the alkyne reveals $k_H/k_D = 1.40(0.1)$, along with evidence of thiol-mediated protonolytic detachment of the vinyl hydrothiolation product from the Sm center. Mechanistic findings indicate turnover-limiting alkyne insertion into the Sm–SR bond, followed by very rapid, thiol-induced Sm-C protonolysis to yield Markovnikov vinyl sulfides with regeneration of the Sm–SR species. A mixture of free radical-derived *anti*-Markovnikov vinyl sulfides is occasionally observed and can be suppressed by γ-terpinene radical inhibitor addition. Metal thiolate complex aggregation to form insoluble species can be delayed kinetically by Cp-based ligation.

In addition, several organoactinide complexes also catalyze the regioselective hydrothiolation of alkynes with various thiols (Scheme 14) [46, 47]. Bond enthalpy considerations for the unexplored reaction predict net exothermicity for RSH addition to alkynes, allenes, and alkenes mediated by organoactinide complexes. While alkyne insertion into the An–S bond (step ii) is predicted to be exothermic,



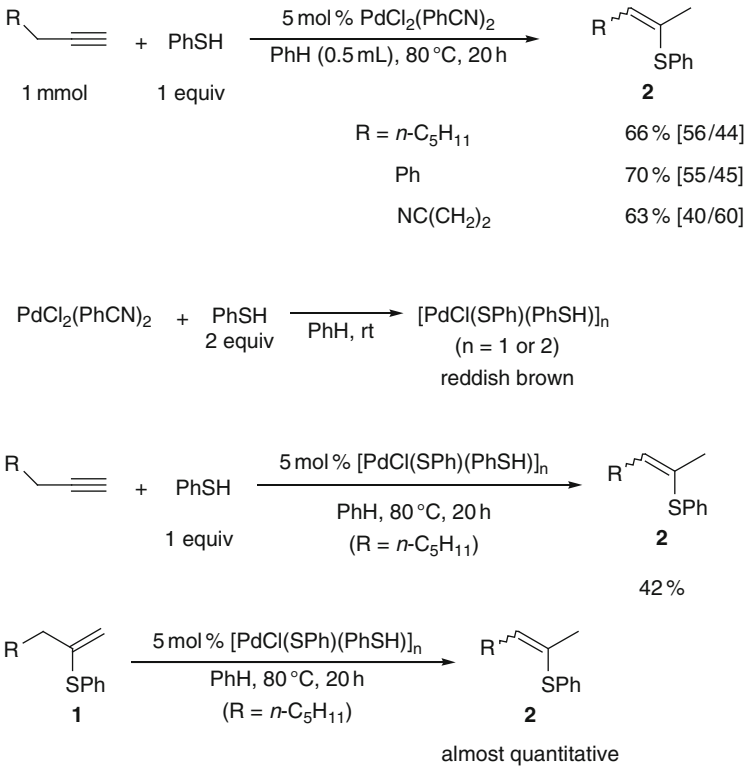
Scheme 14 Organoactinide complexes-catalyzed hydrothiolation of alkynes

alkenes are more challenging, with initial insertions predicted to be endothermic. The final protonolysis (step iii) is estimated to be highly exothermic for all substrates, reflecting the substantial C–H and An–S enthalpies.

2.1.2 Markovnikov Addition and Double-Bond-Isomerization

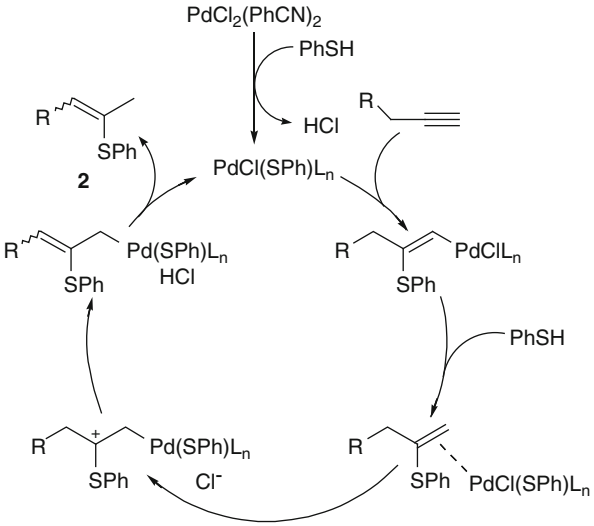
In the transition-metal-catalyzed Markovnikov-type addition of thiols to terminal alkynes, the double-bond-isomerization reactions of the formed Markovnikov addition products **1** are often observed, when the propargylic protons are present in alkynes. As already mentioned, the addition of amines to the reaction systems suppresses the formation of the double-bond-isomerization product **2**. On the other hand, the use of $PdCl_2(PhCN)_2$ as a catalyst causes Markovnikov addition of PhSH to terminal alkynes and the following double-bond-isomerization reaction, which afford 2-phenylsulfanyl-2-alkene **2** as the major product (Scheme 15) [7, 48].

To get some information about this sequential addition/isomerization reaction, the stoichiometric reaction of $PdCl_2(PhCN)_2$ with 2 equiv of PhSH in benzene at room temperature is conducted. The reaction provides a reddish-brown solid of



Scheme 15 $PdCl_2(PhCN)_2$ -catalyzed sequential addition/isomerization reaction

Scheme 16 A catalytic cycle for the sequential addition/isomerization reaction



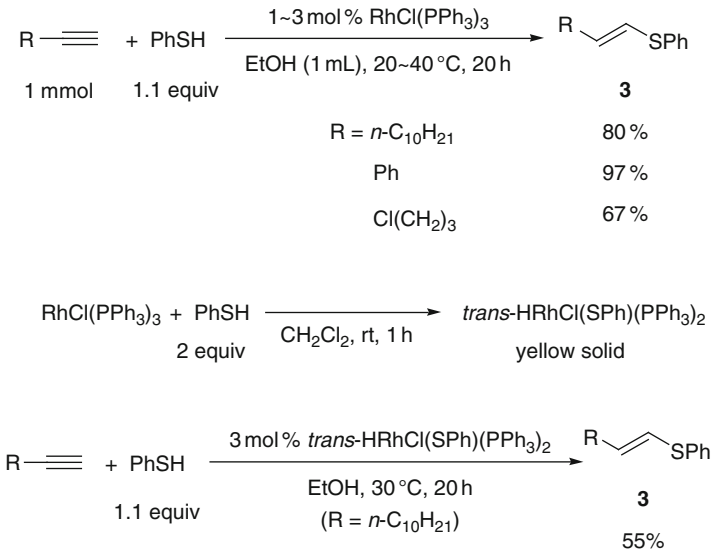
palladium sulfide complex. Elemental analysis and GPC analysis of the reddish-brown solid indicates the formation of $[PdCl(SPh)(PhSH)]_n$ ($n = 1$ or 2). The reddish-brown solid catalyzes the sequential addition/isomerization reaction of 1-octyne, and also the isomerization of Markovnikov adduct **1** to **2**.

A possible catalytic cycle for this sequential addition/isomerization reaction is shown in Scheme 16. Ligand-exchange reaction of $PdCl_2(PhCN)_2$ with PhSH generates $Pd(SPh)ClL_n$, which adds to alkyne providing vinylic palladium intermediate. Protonation of the vinylic palladium intermediate with PhSH to Markovnikov addition product **1**. Double-bond-isomerization proceeds via the cationic intermediate and the allylpalladium intermediate. Protonation of the allylpalladium intermediate with HCl leads to vinyl sulfide **2**. Alternatively, the isomerization may occur by HCl, because HCl in aprotic solvent is a more powerful acid compared with HCl in water. Therefore, tertiary amine may only trap HCl in the reaction system.

As shown in Scheme 3, tetrakis(triphenylphosphine)platinum also indicates high catalytic activity toward the sequential addition/isomerization reaction. In this case, oxidative addition of PhSH to $Pt(PPh_3)_4$ proceeds to give $PtH(SPh)(PPh_3)_2$, which is stable than the corresponding hydropalladium sulfide species. The following hydroplatination and/or thioplatination of alkyne, followed by reductive elimination leads to the Markovnikov adduct **1**. Hydroplatium species can contribute to the isomerization of **1** to **2** [24, 25, 33, 49–53].

2.1.3 *Anti*-Markovnikov Addition

Under radical conditions, thiols add to terminal alkynes to give the corresponding *anti*-Markovnikov addition products **3** regioselectively in good yields. In this



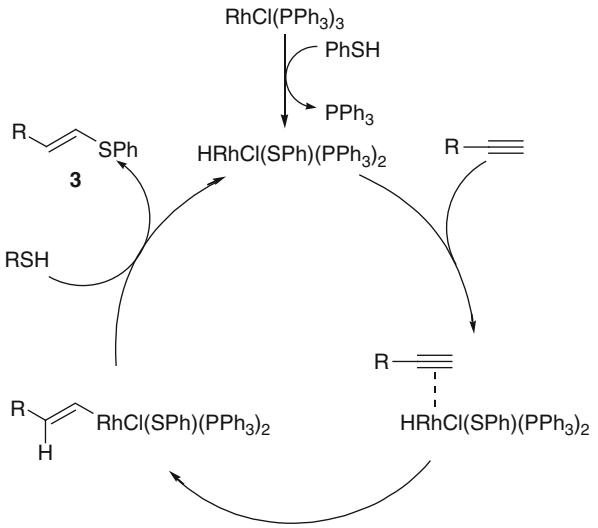
Scheme 17 $RhCl(PPh_3)_3$-catalyzed regio- and stereoselective hydrothiolation

hydrothiolation of alkynes by radical process, however, controlling the stereoselectivity is difficult (a mixture of *E*- and *Z*-isomers are generally formed). Therefore, it is of great importance to attain the regio- and stereoselective hydrothiolation by using transition metal catalysts. Wilkinson's catalyst ($RhCl(PPh_3)_3$) is an excellent catalyst for *anti*-Markovnikov addition of thiols to alkynes with high stereoselectivity (*E*-isomers are obtained selectively) (Scheme 17) [48]. This suggests the $RhCl(PPh_3)_3$-catalyzed hydrothiolation proceeds via *syn*-addition process.

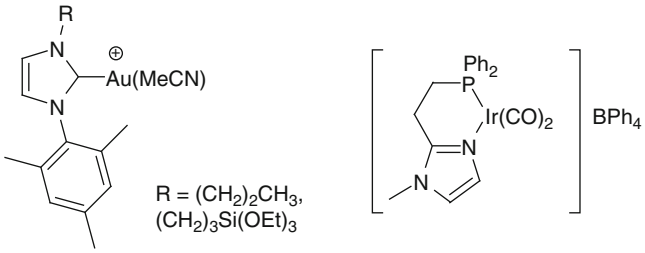
A variety of alkynes undergo regio- and stereoselective hydrothiolation with arenethiols in the presence of $RhCl(PPh_3)_3$. Ethanol and dichlorometane is suitable solvents for this hydrothiolation. This hydrothiolation proceeds well, even when galvinoxyl as a radical inhibitor is added to the reaction system. Recently, Wilkinson's catalyst is reported to be an excellent catalyst for alkyne hydrothiolation with alkanethiols to provide *E*-isomers of *anti*-Markovnikov-type addition products **3** selectively [54].

Equimolar reaction of Wilkinson's catalyst with PhSH is reported to afford *trans*-$HRhCl(SPh)(PPh_3)_2$ as yellow solid [55]. Attempted catalytic hydrothiolation of 1-dodecyne using *trans*-$HRhCl(SPh)(PPh_3)_2$ successfully provides *anti*-Markovnikov adduct **3** selectively.

To gain further insight into the mechanism, the reaction of *trans*-$HRhCl(SPh)(PPh_3)_2$ with an equimolar amount of 1-dodecyne is monitored by ^1H NMR. The reaction leads to the disappearance of both Rh–H (δ-16.4) and acetylenic H, and instead, a new doublet peak appeared at δ 5.1 (probably as the vinylic proton). The new peak does not disappear after standing for 20 h at room temperature, but the addition of PhSH (1equiv) to the solution leads to the formation of the corresponding vinylic sulfide after standing for 6 h.



Scheme 18 A catalytic cycle for the $RhCl(PPh_3)_3$-catalyed hydrothiolation



Scheme 19 Gold catalyst and iridium catalyst for hydrothiolation of alkynes

Based on these observations, a possible catalytic cycle for the rhodium-catalyzed *anti*-Markovnikov addition of thiols to alkynes is shown in Scheme 18. Oxidative addition of PhSH to Wilkinson's catalyst generates hydrorhodium sulfide species (*trans*-$HRhCl(SPh)(PPh_3)_2$). After coordination of alkyne to the hydrorhodium sulfide species, stereoselective insertion of alkyne into Rh–H bond provides *E*-isomer of vinylic rhodium intermediate. The subsequent reductive elimination of *anti*-Markovnikov adduct in the presence of PhSH regenerates the hydrorhodium sulfide species.

Cationic gold complexes are useful catalysts for *anti*-Markovnikov-type hydrothiolation with excellent regio- and stereoselectivities (Scheme 19) [56].

Rhodium and iridium complexes bearing bidentate N,N and N,P ligands also indicate the catalytic activity for regioselective hydrothiolation. In this reaction, *anti*-Markovnikov-type adducts are obtained as a stereoisomeric mixture (Scheme 19) [57, 58].

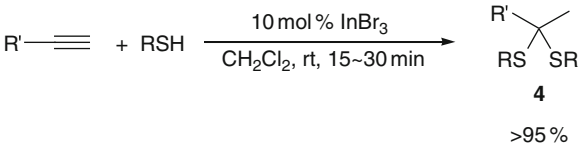
Several synthetic methods of *anti*-Markovnikov-type hydrothiolation products by using transition metal catalysts are reported [59–64]. For example, treatment of

alkynes with alkanethiols in the presence of cesium carbonate (Cs_2CO_3) and radical inhibitor in DMSO provides the corresponding adduct, (*Z*)-1-alkenyl alkyl sulfides, in good yield with high selectivity [59]. In the presence of CuI and Cs_2CO_3, a variety of thiols reacted with arylpropiolic acids to afford the corresponding vinyl sulfides with high stereoselectivity for *Z*-isomer [60]. The combination of CuI and Cs_2CO_3 with rongalite is effective for the hydrothiolation of alkynes with diaryl disulfides, leading to (*Z*)-1-alkenyl sulfides stereoselectively [61]. Hydrothiolation of alkynes using Al_2O_3/KF under solvent-free conditions provides *anti*-Markovnikov-type vinyl sulfides as stereoisomeric mixtures [62]. Some of these reactions proceed via the formation of anionic intermediates by the nucleophilic attack of metal sulfides to unsaturated compounds. Electron transfer process from thiols to manganese acetate generates sulfanyl radicals and then addition of the sulfanyl radicals to alkynes provides (*E*)-vinyl sulfides preferentially [63]. These methods are alternative access to the *anti*-Markovnikov-type vinylic sulfides.

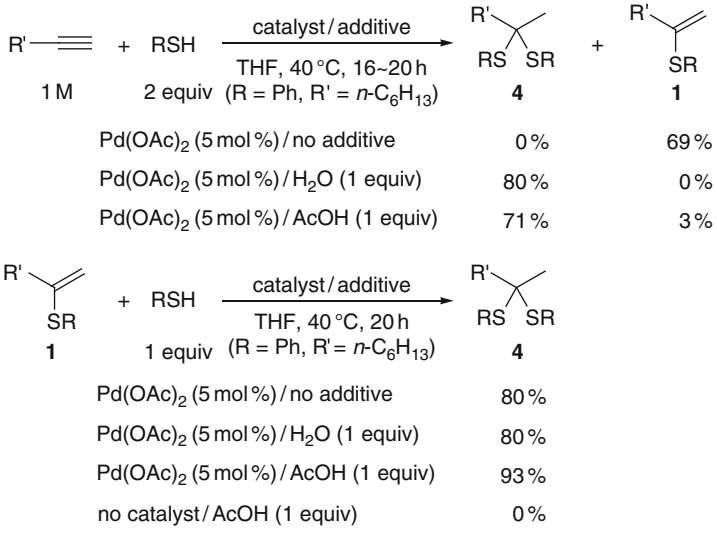
2.1.4 Double Hydrothiolation

In the transition-metal-catalyzed hydrothiolation reactions, dithioketals **4** as double thiolation products are sometimes formed as byproducts. Since dithioketals **4** are synthetically useful as carbonyl equivalents, selective synthesis of **4** from alkynes and thiols is attractive. Indium bromide ($InBr_3$) as a water-tolerant green Lewis acid catalyst is found to catalyze efficiently the hydrothiolation of alkynes with arene- and alkanethiols to produce the corresponding dithioketals in excellent yields (Scheme 20) [64].

As mentioned in Sect. 2.1.1.1, palladium diacetate ($Pd(OAc)_2$) is a useful catalyst for the hydrothiolation of alkynes to give Markovnikov-type vinyl sulfides **1**. Interestingly, when the same palladium-catalyzed reaction is conducted using 2 equivalents of thiols in the presence of water or acetic acid (1 equiv), the Markovnikov-type vinyl sulfides **1** is not formed, and instead dithioketals **4** is obtained selectively (Scheme 21) [65]. The $Pd(OAc)_2$-catalyzed reaction of **1** with equimolar amounts of thiol provides **4** in good yield, whereas no reaction is observed in the absence of $Pd(OAc)_2$. These results suggest the intermediacy of vinyl sulfides **1**. Recently, noncatalytic double addition of thiols to alkynes in water is reported to afford the corresponding vicinal dithioalkanes, regioselectively [66]. Therefore, the present $Pd(OAc)_2$-catalyzed double addition of thiols to alkynes, which affords the geminal dithioalkanes, is regiocomplementary to the noncatalytic reaction.



Scheme 20 $InBr_3$-catalyzed double hydrothiolation leading to dithioketals



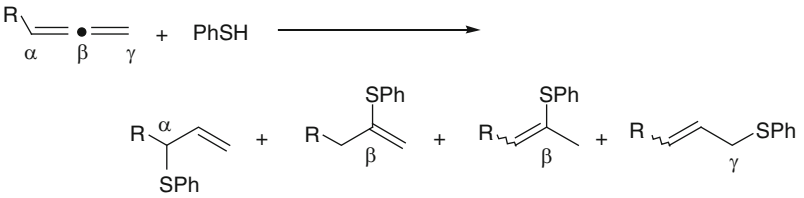
Scheme 21 $Pd(OAc)_2$-catalyzed double hydrothiolation leading to dithioketals

2.2 Hydrothiolation of Allenes

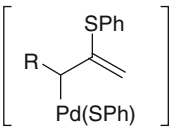
In the Sect. 2.1, a variety of transition-metal-catalyzed hydrothiolation reactions of alkynes with thiols have been described. Transition metal catalysts are clearly useful for the regio- and/or stereoselective addition of thiols to carbon–carbon triple bonds. In contrast, the transition-metal-catalyzed addition of thiols to carbon–carbon double bonds such as alkenes has not been developed hitherto, except for Lewis acid-catalyzed hydrothiolation [8, 67–72]. This is most probably due to the lower coordination ability of alkenes compared with alkynes, which may permit the polymerization of metal sulfide complexes, resulting in inactivation of them as key catalysts for hydrothiolation.

Since allenes have higher coordination ability and are reactive compared with alkenes, the transition-metal-catalyzed addition of thiols to the carbon–carbon double bonds is expected to proceed. Indeed, several transition metal complexes exhibit catalytic activity toward the addition of thiols to allenes. Of great importance in the addition of thiols to allenes is controlling the selectivity. Formally, four regioisomers are considered in the addition of thiols to terminal allenes (Scheme 22). In the radical addition of benzenethiol to terminal allenes initiated by molecular oxygen, the formed thio radical adds to both the inner and terminal carbon of allenes, affording a mixture of vinyl and allyl sulfides [73].

In contrast, palladium acetate ($Pd(OAc)_2$) indicates an excellent catalytic activity for the regioselective addition of thiols to the inner double bond of terminal allenes, providing the corresponding 2-sulfanyl-1-alkenes in good yields [74]. A possible pathway for this allene hydrothiolation may involve the following processes: (i) ligand-exchange reaction between $Pd(OAc)_2$ and PhSH (2 equiv)



(R = *t*-Bu)				
O_2	–	38 %	37 %	25%
$Pd(OAc)_2$*1	–	85 %	–	–
(R = *c*-Hex)				
$Pd(PPh_3)_4$*2	–	82 %	–	–
$Pt(PPh_3)_4$*3	–	3 %	58 %	–



*1$Pd(OAc)_2$ (2 mol %), THF, reflux, 2 h.
*2$Pd(PPh_3)_4$ (5 mol %), MeCN, reflux, 12 h.
*3$Pt(PPh_3)_4$ (5 mol %), MeCN, 40 °C, 36 h.

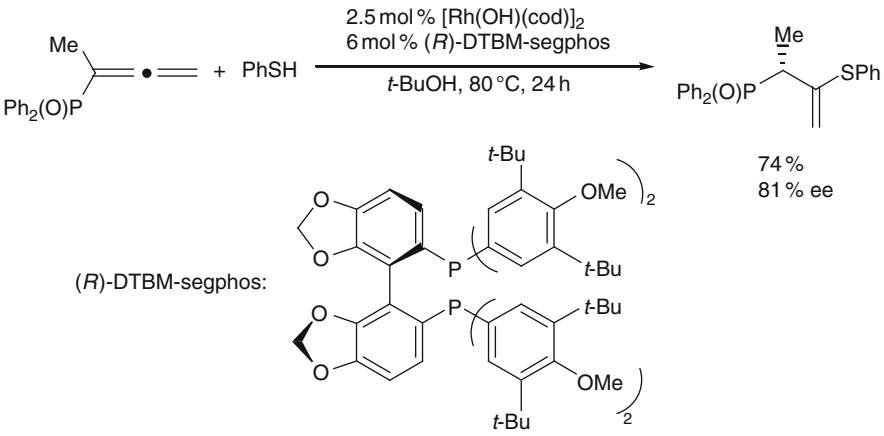
Scheme 22 Hydrothiolation of allenes

generates $Pd(SPh)_2$ along with AcOH (2 equiv); (ii) Since $Pd(SPh)_2$ is a divalent species, thiopalladation takes place at the relatively electron-rich double bond, i.e., inner double bond of allenes, leading to the allylic palladium intermediate; (iii) protonation of the allylic palladium intermediate with PhSH affords the vinyl sulfide with regeneration of $Pd(SPh)_2$. $Pd(PPh_3)_4$ also exhibits similar regioselectivity as $Pd(OAc)_2$, whereas $Pt(PPh_3)_4$ shows different regioselectivity [75]. 2-Sulfanyl-1-alkenes can be synthesized alternatively by the $Pd(PPh_3)_4$-catalyzed hydrothiolation of allenes with diphenyl disulfide in the presence of PPh_3 and H_2O. $(PhS)_2$ reacts with PPh_3 and H_2O to generate PhSH in situ [76].

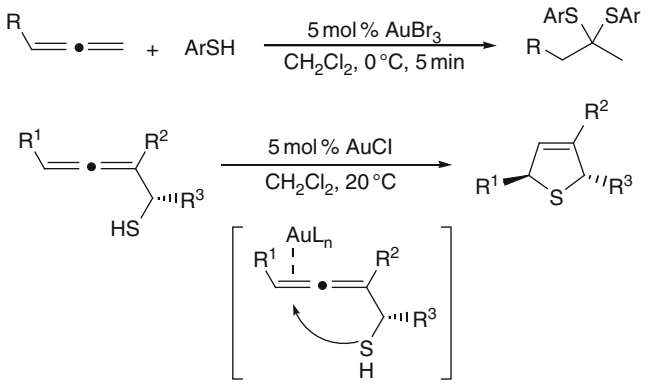
Rhodium-catalyzed asymmetric hydrothiolation of diphenylphosphinylallenes is reported (Scheme 23) [77].

Reaction of dialkyl disulfide with allenes is catalyzed by a rhodium–phosphine complex and trifluoromethanesulfonic acid giving (*E*)-2-alkylthio-1,3-dienes [78]. $AuBr_3$-catalyzed regioselective hydrothiolation of aromatic allenes with arenethiols affords the corresponding dithioketals in good yields under mild conditions [79]. Intramolecular hydrothiolation of α-thioallenes to 2,5-dihydrothiophenes is successfully catalyzed by AuCl (Scheme 24) [80].

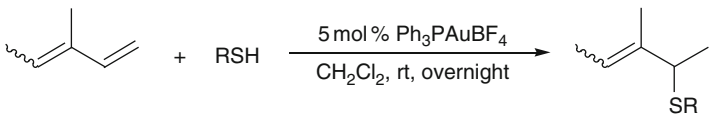
This cyclization reaction may proceed via the coordination of the double bond of allenes to Au and the following nucleophilic attack of sulfur to the activated double bond.



Scheme 23 Asymmetric hydrothiolation of diphenylphosphinylallenes



Scheme 24 Gold-catalyzed hydrothiolation of allenes



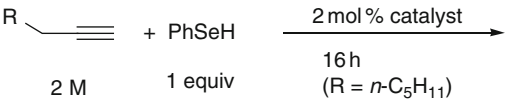
Scheme 25 Gold-catalyzed hydrothiolation of conjugated dienes

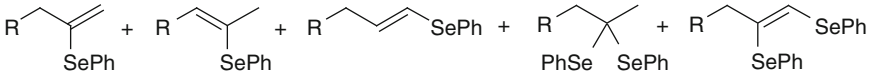
The thiol additions to conjugated dienes are catalyzed by gold complexes, Ph_3PAuBF_4, with excellent yields at room temperature (Scheme 25) [81]. This hydrothiolation occurs regioselectively at the less electron-rich double bond of conjugated dienes.

3 Transition-Metal-Catalyzed Hydroselenation with Selenols

Benzeneselenol as a representative selenol is a colorless liquid of greater acidity than benzenethiol (p*K*a = 5.9 (PhSeH); 6.5 (PhSH)). The bond energy of Se–H is 73 kcal/mol, is smaller than S–H (87 kcal/mol) [82]. These properties may contribute to the efficiency in the oxidative addition of selenols to low-valent transition metals, ligand-exchange reaction between high-valent transition metal complexes and selenols, and protonation process of carbon-metal bonds. Indeed, several transition metal complexes catalyze the highly selective hydrothiolation of alkynes and allenes.

Representative results of the transition-metal-catalyzed addition of benzeneselenol to 1-octyne are shown in Scheme 26 [83–85]. Similarly as the hydrothiolation of alkynes, $Pd(OAc)_2$ is an active catalyst for the Markovnikov-type hydroselenation of alkynes with PhSeH, but the product selectivity is somewhat lower compared with the hydrothiolation. However, the use of pyridine as solvent or the addition of 2,2'-bipyridyl as ligand attains the excellent product selectivity giving the Markovnikov-type vinyl selenides **6** in good yields. When $PdCl_2(PPh_3)_2$ is employed as the catalyst, the sequential addition/isomerization reaction takes place selectively to give the vinyl selenides **7** as a stereoisomeric mixture. Although the $RhCl(PPh_3)_3$-catalyzed hydrothiolation provides *anti*-Markovnikov-type adduct regioselectively,





6 **7** **8** **9** **10**

	6	7	8	9	10
$Pd(OAc)_2$, PhH, 80 °C	62%	7%	<3%	13%	—
$Pd(OAc)_2$, pyridine, 100 °C	77%	—	—	—	—
$Pd(OAc)_2$, PhMe, 100 °C	63%	—	—	—	—
2, 2'-bipyridyl (20 mol%)					
$PdCl_2(PPh_3)_2$, PhH, 80 °C	4%	71% [62/38][a]	—	—	3%
$RhCl(PPh_3)_3$, PhH, 80 °C	7%	55% [64/36][a]	—	—	—

[a] *E*/*Z* ratio.

Scheme 26 Transition-metal-catalyzed hydrothiolation of alkynes

the sequential addition/isomerization reaction proceeds preferentially in the case of the hydroselenation with PhSeH.

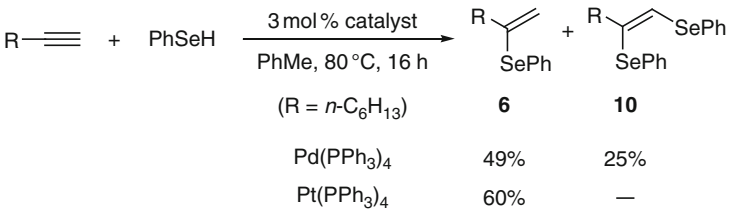
In the cases of aromatic alkynes, the radical addition of PhSeH induced by oxygen (or air) is a very fast process (the addition is finished immediately after mixing the alkynes and PhSeH), giving *anti*-Markovnikov adduct regioselectively. The key species, PhSe·, adds to alkynes to generate vinyl radicals. α-Aryl-substituted vinyl radicals (formed by the addition of PhSe· to aromatic alkynes) are among π-radicals and more stable than α-alkyl-substituted vinyl radicals as σ-radicals (formed by the addition of PhSe· to aliphatic alkynes) [86]. Therefore, it is relatively difficult, compared with the hydrothiolation, to control the selectivity in transition-metal-catalyzed hydroselenation of aromatic alkynes.

The catalytic ability of low-valent palladium and platinum complexes bearing phosphines as ligands toward the hydroselenation is investigated in detail (Scheme 27) [87, 88]. The $Pd(PPh_3)_4$-catalyzed reactions of alkynes with PhSeH provides Markovnikov-type hydroselenation products **6** and bisselenation products **10**, whereas $Pt(PPh_3)_4$ selectively provides only Markovnikov-type hydroselenation products **6**.

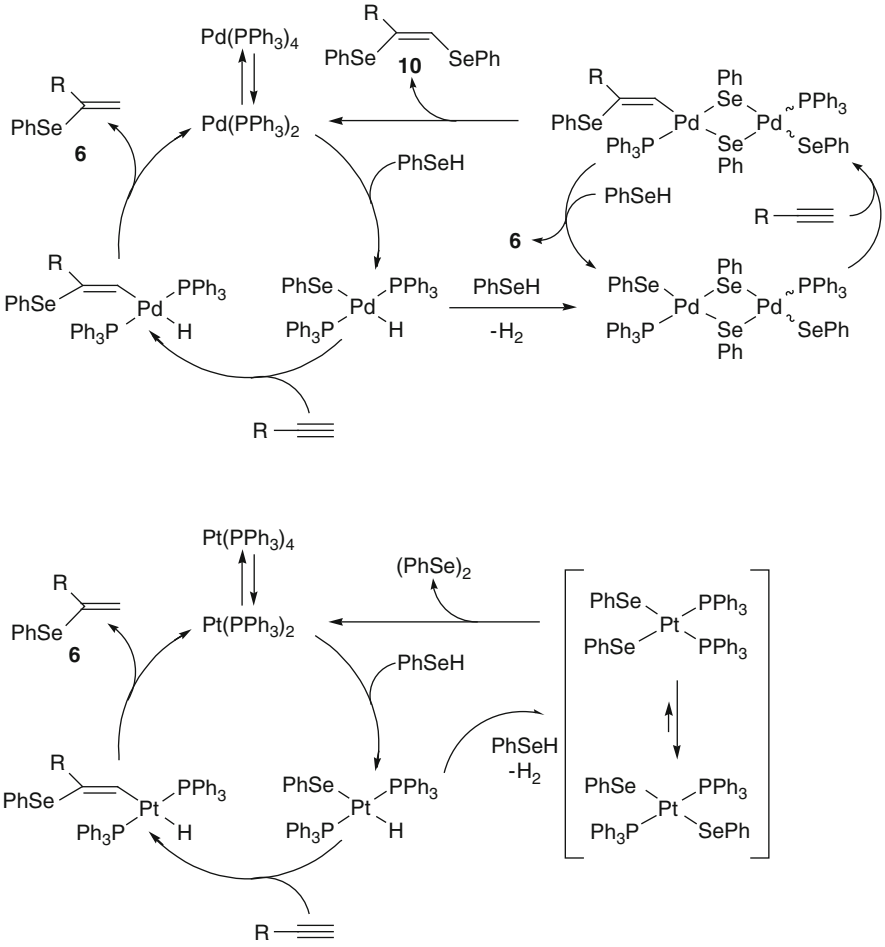
In both cases, oxidative addition of PhSeH to Pd or Pt complexes generates HM $(SePh)(PPh_3)_2$ (M = Pd or Pt), which further reacts with PhSeH to give palladium or platinum selenides [89] (Scheme 28) (Several related works about the oxidative addition and metal selenides are reported [89–92]). Palladium sulfides easily undergoes dimerization to form the corresponding selenium-bridged dinuclear complexes, whereas, in the case of Pt, the rapid isomerization of *cis*-[Pt $(SePh)_2(PPh_3)_2$] to *tarns*-[$Pt(SePh)_2(PPh_3)_2$] avoids such dimerization, leading to the reductive elimination to $(PhSe)_2$. The C–H bond formation in palladium-catalyzed transformation most likely is an intermolecular trapping of σ-vinyl intermediates with PhSeH, in contrast to intramolecular reductive elimination occurring when platinum catalyst is used.

A simple heterogeneous nickel-based catalytic methodology is developed for regioselective hydroselenation of terminal alkynes (selective Markovnikov-type addition) and stereoselective hydroselenation of internal alkynes (selective *syn*-addition) [93]. The catalytic transformation is performed under mild conditions, thus avoiding byproduct formation.

The mechanistic study revealed that the yield of the hydroselenation products depends on the catalyst particle size. The catalysts prepared from the precursor catalysts and selenols have the same chemical formula $[M(SeAr)_2]_n$, but the sizes of



Scheme 27 Low-valent transition-metal-catalyzed hydroselenation of alkynes



Scheme 28 Catalytic cycles for Pd- and Pt-catalyzed hydroselenations

the particles differed dramatically. Poor results are obtained for $NiCl_2$ precursor, which gave catalyst particle sizes of 3–10 μm. Better results are observed with Pd $(OAc)_2$ and $Ni(OAc)_2$ precursors, with particles sizes of 3–6 μm and 2–5 μm, respectively. Further higher catalytic activity is observed in a heterogeneous catalytic system of $NiCl_2$ in the presence of Et_3N, and the particle sizes are 0.3–1.5 μm. The best results are achieved with $Ni(acac)_2$ and the catalytic activity rapidly increases upon decreasing particle size into the nanosized region (the sizes of the nanoparticle from $Ni(acac)_2$ are 300 ± 90 nm) [17]. Some related nickel-catalyzed selenation reactions of unsaturated compounds are reported [94, 95].

Indium(I) iodide is found to promote the regio- and stereoselective hydrothiolation of propargyl alcohols with $(PhSe)_2$ (Markovnikov-type addition and *anti*-addition)

[96]. In addition, regioselective Markovnikov hydroselenation of terminal alkynes using indium(III) selenates is also reported [97].

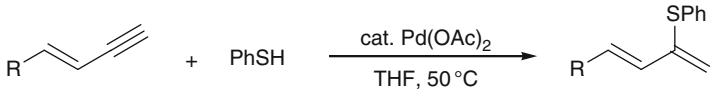
The $Pd(OAc)_2$-catalyzed hydroselenation of alkynes with PhSeH can be applied to the hydroselenation of allenes [98]. In the cases of terminal allenes, the corresponding 2-selanyl-1-alkenes are obtained preferentially, whereas the radical addition of PhSeH to terminal allenes affords 2-selanyl-2-alkenes as the major product [99].

4 Applications to the Synthesis of Functionalized Sulfur Compounds

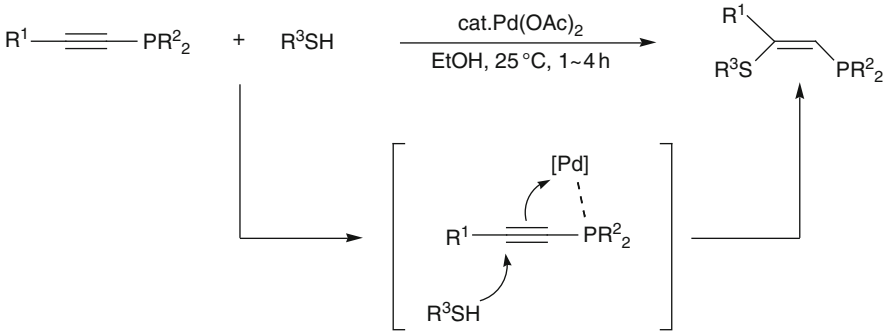
Catalytic hydrothiolation and hydroselenation reactions are very useful for providing a wide variety of functionalized organosulfur and selenium compounds. For example, the palladium-catalyzed hydrothiolation of conjugated enynes affords a series of 2-(phenylsulfanyl)-1,3-dienes regioselectively in good yields (Scheme 29) [100].

Palladium-catalyzed hydrothiolation of alkynylphosphines proceeds via *anti*-addition process, yielding the corresponding (*Z*)-1-phosphino-2-thioalkenes regio- and stereoselectively. The coordination of the phosphino group to the palladium induces the rare example of catalytic *anti*-addition of thiols to alkynes (Scheme 30) [101].

A novel palladium-catalyzed thioboration of terminal alkynes (RC≡CH) with $PhSBR'_2$ provides (*Z*)-2-sulfanyl-1-alkenylboranes (R(PhS)C=CH-BR'_2)



Scheme 29 Palladium-catalyzed hydrothiolation of conjugated enynes

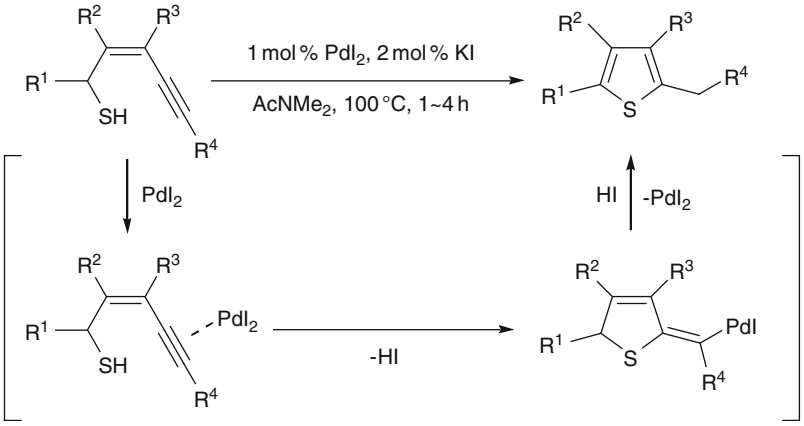


Scheme 30 Palladium-catalyzed hydrothiolation of alkynylphosphines

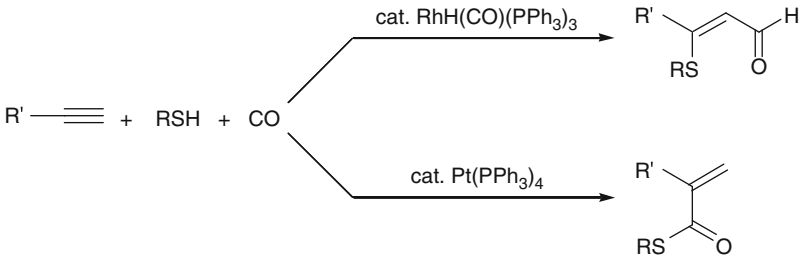
regio- and stereoselectively, the methanolysis of which affords the corresponding 2-sulfanyl-1-alkenes (R(PhS)C = CH_2) as hydrothiolation products [102].

The palladium-catalyzed intramolecular hydrothiolation of (*Z*)-2-en-4-yne-1-thiols, followed by double-bond-isomerization successfully provides substituted thiophenes in good yields. The hydrothiolation step may involve the nucleophilic attack of the sulfanyl group to the carbon–carbon triple bond coordinated by palladium (Scheme 31) [103].

When the transition-metal-catalyzed hydrothiolation of unsaturated compounds is performed in the presence of carbon monoxide, carbonylation reactions may proceed with the introduction of sulfanyl groups. In fact, a series of carbonylative thiolation reactions of alkynes and allenes are reported. These reactions provide useful tools to synthetically important organosulfur compounds [104, 105]. For example, the rhodium-catalyzed reaction of alkynes with thiols and CO provides the corresponding thioformylation products regioselectively [106, 107]. Switching the catalyst from rhodium complex to platinum complex leads to a sharp reversal of regioselectivity of CO introduction [108, 109] (Scheme 32).



Scheme 31 Thiophene synthesis by palladium-catalyzed hydrothiolation



Scheme 32 Regioselective carbonylative thiolation of alkynes

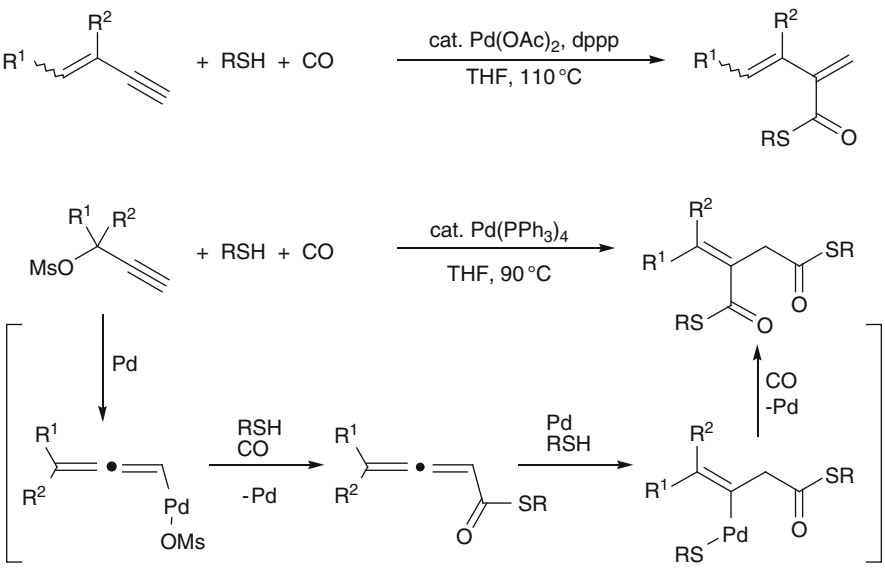
In the former reaction, $[Rh(SR)(CO)(PPh_3)_2]_n$ is formed as a key species by the reaction of $RhH(CO)(PPh_3)_3$ with RSH along with the release of H_2. Regioselective thiorhodation of alkynes with $Rh(SR)(CO)(PPh_3)_2$ generates vinylrhodium intermediate (R'(RS)C=CH–$Rh(CO)(PPh_3)_2$), and the following CO insertion into the C–Rh bond forms acylrhodium intermediate. The acylrhodium intermediate reacts with RSH to afford the corresponding thioformylation products with recovery of $Rh(SR)(CO)(PPh_3)_2$.

The latter carbonylation involves the formation of $PtH(SR)(PPh_3)_2$ by the oxidative addition of RSH to the zero-valent platinum complex. A possible pathway may include the CO insertion into the S–Pt bond of $PtH(SR)(PPh_3)_2$. Then, acylplatination of alkynes generates β-thiocarbonyl-substituted vinylplatinum intermediate, which undergoes reductive elimination to give the α,β-unsaturated thioesters with regeneration of the catalyst.

β-Sulfanyl-α,β-unsaturated carbonyl compounds like the thioformylation products are structurally interesting, because the *n*-σ* interaction between the sulfanyl group and carbonyl group are observed [110].

Conjugated enynes undergo regioselective thiocarbonylation successfully giving the corresponding thioesters bearing dienyl substituents (Scheme 33) [111].

Furthermore, highly stereoselective dithiocarbonylation of propargylic mesylates with thiols and carbon monoxide is attained by the use of tetrakis(triphenylphosphine)palladium(0) as the catalyst. This dithiocarbonylation is believed to proceed via allenylpalladium and allenyl thioesters, and the high stereoselectivity may be rationalized by a mechanism where nucleophilic attack of a Pd(0) species on the



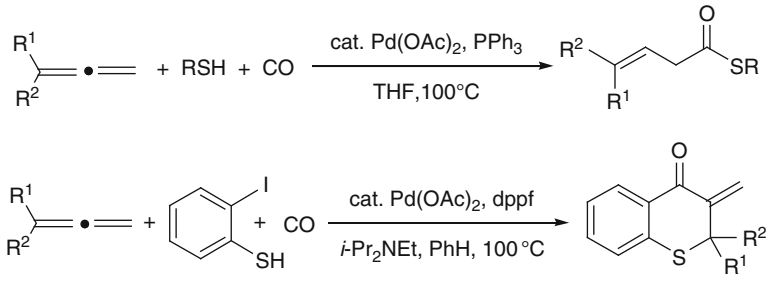
Scheme 33 Regioselective thiocarbonylation of alkynes

allenyl *sp* carbon occurs from the less hindered side of an alkyl substituent (bulkiness of the substituents: $R^2 > R^1$) [112].

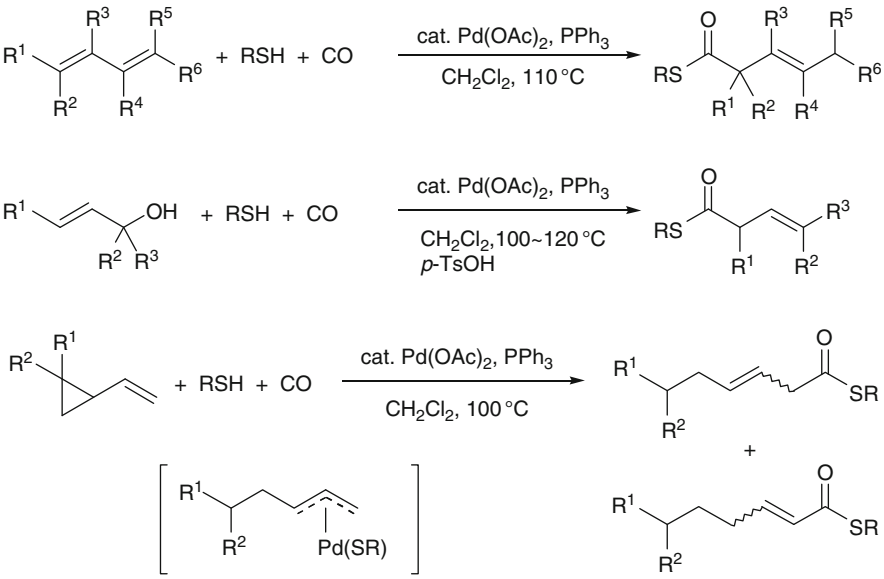
In the cases of propargyl and homopropargyl alcohols, carbonylative lactonization proceeds to give α,β-unsaturated lactones in good yields [112–114].

Allenes also undergo highly regioselective thiocarbonylation with thiols and carbon monoxide in the presence of palladium catalysts. The use of $Pd(OAc)_2/PPh_3$ as the catalyst leads to the selective formation of β,γ-unsaturated thioesters (Scheme 34) [115].

Platinum(0) complexes such as $Pt(PPh_3)_4$ also catalyze carbonylative thiolation of allenes, affording α,β- and β,γ-unsaturated thioesters in good yields [116]. When 2-iodobenzenethiols are employed for the palladium-catalyzed carbonylation with



Scheme 34 Regioselective thiocarbonylation of allenes



Scheme 35 Regioselective thiocarbonylation of C–C double-bond compounds

allenes, thiochroman-4-ones are obtained in good to excellent yields with high regioselectivity [117].

The $Pd(OAc)_2/PPh_3$ catalyst is very useful for the thiocarbonylation of a variety of carbon–carbon double-bond compounds such as conjugated dienes [118], allylic alcohols [119], and vinylcyclopropanes [120], as shown in Scheme 35. These reactions proceeds via π-allylpalladium complexes as key intermediates. Furthermore, a catalytic system based on $Pd(OAc)_2$/(*R*,*R*)-DIOP is found to effect asymmetric thiocarbonylation of prochiral 1,3-dienes to produce good yields of optically enriched β,γ-unsaturated thioesters [121].

5 Conclusions

In this chapter, recent advance in the transition-metal-catalyzed hydrothiolation and hydroselenation of alkynes, allenes, and related compounds has been described. Although organosulfur and selenium compounds are believed to be catalyst poisons, these new reactions described in this chapter clearly indicate the efficacy of transition metal catalysts in the synthetic reactions of organosulfur and selenium compounds. The use of transition metal catalysts makes it possible to attain highly regio- and stereoselective synthesis of a variety of vinylic and allylic sulfides and selenides. These reactions are very useful in terms of not only the organosulfur and selenium compounds synthesis but also the development of bioactive compounds and new materials. For example, π-conjugated polymers including heteroatoms [101, 122] are promising in material science and these research fields require the highly selective methods for introduction of heteroatom groups involving sulfur and selenium.

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