

# Organometallic catalysts in synthetic organic chemistry: From reactions in aqueous media to gold catalysis\*

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*Abstract:* Water has attracted significant attention as an alternative solvent for transition-metal-catalyzed reactions. The use of water as solvent allows simplified procedures for separation of the catalyst from the products and recycling of the catalyst. Water is an inexpensive reagent for the formation of oxygen-containing products such as alcohols. The use of water as a medium for promoting organometallic and organic reactions is also of great potential. This chapter will focus on old and recent developments in the design and applications of some catalytic reactions using aqueous-phase Pd, Rh, Pt, and Au complexes.

*Keywords:* water; catalysis; palladium; gold; rhodium; potassium organotrifluoroborates; asymmetric 1,4-addition; recycling.

## INTRODUCTION

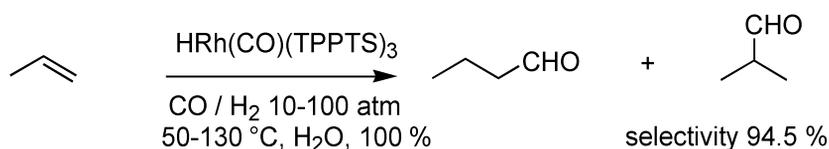
Over the past few years, significant research has been directed toward the development of new technologies for environmentally benign processes. The use of water as solvent in homogeneous metal-catalyzed reactions has gained increasing attention because of the potential environmental and economic benefits of replacing organic solvents with water. Indeed, water is an attractive solvent because it is inexpensive and nontoxic; the most attractive feature is its utility in the development of green and environmentally safe processes [1]. The complexes (M<sub>t</sub>L<sub>n</sub>) applied as catalyst gain their water solubility by incorporation of a strongly hydrophilic phosphane ligand. Thus, water can simplify catalyst separation by creating a biphasic system. The first water-soluble mono *m*-sulfonated phosphane (TPPMS), **1**, was reported in 1958 by Ahrland et al. [2]. In the late 1970s, Kuntz designed the *m*-trisulfonated triphosphine (TPPTS), **2** [3a]. This highly soluble phosphane has been used for a wide variety of chemical processes, particularly in the large-scale hydroformylation of propene to butyraldehyde by Ruhrchemie/Rhone-Poulenc (Scheme 1) [3b].

Casalnuovo et al. were the first to apply water-soluble ligands for cross-coupling reactions using preformed Pd (TPPMS)<sub>3</sub> in water/acetonitrile [4a]. In 1992, Genêt et al. reported a highly efficient water-soluble Pd(0) produced in situ from Pd(OAc)<sub>2</sub> and TPPTS; for example, it has been shown that in aqueous-organic medium, cross-coupling of aryl iodides with terminal alkynes is achieved without Cu additive [4b]. At that time, only a few dozen references existed in the literature on this subject. A

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Scheme 1

growing number of academic and industrial groups have worked to develop effective, aqueous-phase catalyzed reactions since these early reports. Now, organic reactions in water have become the most exciting research endeavors. In one decade, several books and reviews have been published [5,6].

### ACHIRAL WATER-SOLUBLE PHOSPHANES

Since the discovery of TPPMS (1) and TPPTS (2), several groups have worked intensively to prepare new water-soluble phosphines. The use of ligands providing the ability to fine-tune the reactivity, selectivity, and solubility of the catalyst system is of great interest. For these reasons, a wide range of hydrophilic ligands, such as modified sulfonated phosphines, have been designed [7]. It is also possible to induce hydrophilicity in phosphine ligands by substituting them with guanidinium (3) [8], phosphonate (4) [9], and carboxylate (5) [10] groups (Fig. 1).

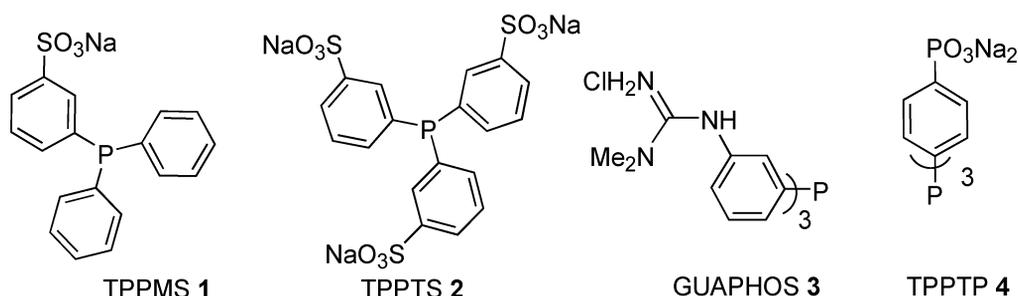
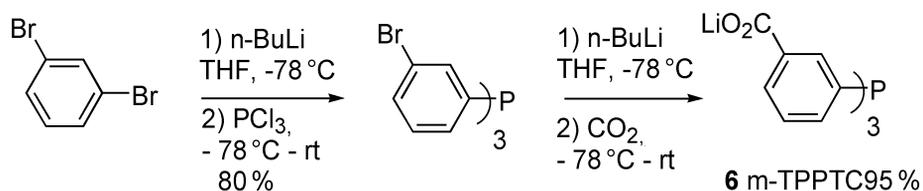


Fig. 1 Selected achiral water-soluble ligands.

Recently, we have reported a versatile preparation of the water-soluble *m*-TPPTC (6) [11]. Commercially available 1,3-dibromobenzene was cleanly monolithiated and reacted with phosphorous trichloride leading to tris-*meta* bromotriphenyl phosphine in quantitative yield. Then the lithiated trianion was formed at  $-78\text{ }^\circ\text{C}$  and quenched by dry ice, leading to *m*-TPPTC (Scheme 2). The synthesis is short and can be scaled up easily. The water solubility of *m*-TPPTC was found to be 1100 g/l of water and is similar to TPPTS.



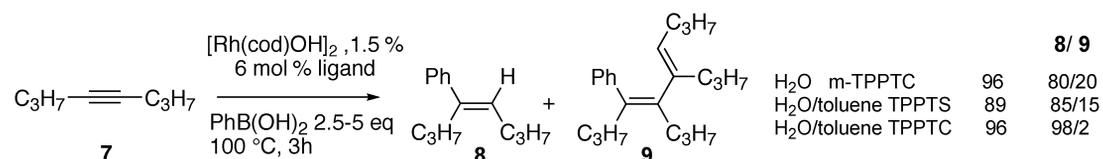
Scheme 2

We compared the steric and electronic properties of this new ligand with TPPTS. As expected, both ligands have the same cone angle, 166°. We also have established that *m*-TPPTC phosphane is more electron-rich than the sulfonated analog. Interfacial tension measurement performed with TPPTS and TPPTC clearly revealed two different behaviors [12]. TPPTS is a hydrotropic compound, whereas TPPTC behaves as a surface-active compound. These features induce higher efficiency of TPPTC vs. TPPTS in Rh-arylation reactions [11b,c].

## METAL-CATALYZED REACTIONS WITH TRIVALENT ORGANOBORON COMPOUNDS IN AQUEOUS MEDIUM

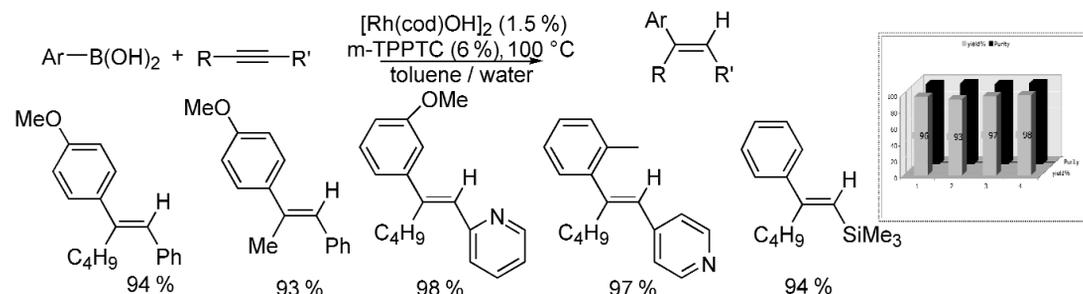
Since the discovery of Suzuki–Miyaura (SM), organoboron compounds have emerged as the reagents of choice in various transition-metal-catalyzed reactions. Hayashi's group has reported Rh-catalyzed addition of boronic acids to alkynes in dioxane water using Rh/diphenyl phosphane system for the first time [13].

There was one system described in water requiring basic conditions and the presence of a surfactant. It has been reported that alkynyl hetero aromatic compounds reacted with aryl boronic acids to give trisubstituted olefins in the presence of  $[\text{Rh}(\text{COD})\text{Cl}]_2$  with pyridine-substituted water-soluble phosphane [14]. This system was very specific and limited to 2-alkynyl pyridyl substrates, and the use of the well-known hydrophilic sulfonated phosphane TPPTS was ineffective. We have found that  $[\text{Rh}(\text{COD})\text{OH}]_2$  in the presence of TPPTC in pure water promotes the hydroarylation of 4-octyne (**7**) with formation of a mixture of the trisubstituted alkene (**8**) with a significant amount of diene (**9**) (Scheme 3).



Scheme 3

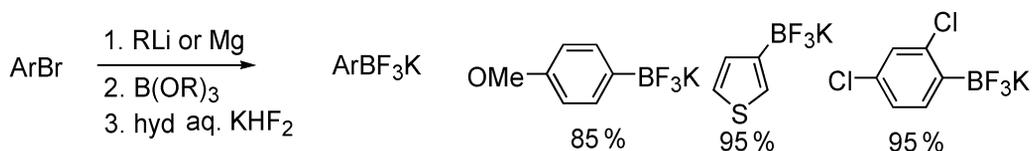
Speculating that the hydrophobic effect on pure water may promote a second addition of the alkyne, as several alkynes are close to each other, we used a biphasic system toluene/water in order to control the concentration of the alkynes [15]. Indeed, under biphasic conditions we found that the desired alkene was isolated in high yield and selectivity (Scheme 4). The scope and versatility of the reaction are wide and totally regioselective for alkyl-aryl alkynes, including heteroaromatic alkynes. In addition, the Rh/*m*-TPPTC system was recycled three times in water/toluene without loss of the activity and with excellent purity of the trisubstituted alkenes [16].



Scheme 4

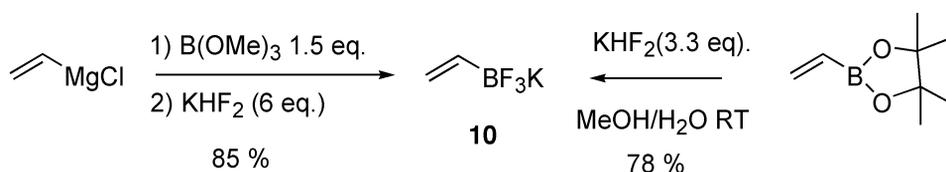
## POTASSIUM ORGANOTRIFLUOROBORATES: SYNTHESIS

The increased number of applications of trivalent organoboranes, particularly boronic acids and esters, relies on the ready availability of these reagents via transmetalation or hydroboration reactions. However, many organoboranes are not highly stable, particularly alkyl- and alkynylboranes. The lack of stability of organoboranes is due to the vacant orbital on boron, which can be attacked by oxygen or water, resulting in the decomposition of the reagent. One solution emerged in the 1960s with the use of potassium organotrifluoroborates. The development of potassium organotrifluoroborate chemistry in organic synthesis started with the improvement in their preparation procedures. It is only in 1995 that a highly efficient method using potassium hydrogen difluoride ( $\text{KHF}_2$ ) as fluorinating agent of trivalent boron reagents was described by Vedejs [22]. In 2003, in a short review we reported the principal application of potassium organotrifluoroborates in organic synthesis [18]. Since that date, where only limited papers were published on these emerging compounds, an increased number of publications and patents on that topic have been reported in the literature [19–21]. We have reported that the preparation of potassium organotrifluoroborates does not require the use of purified organoboronic acids [22]. These three steps of a one-pot procedure proved to be very efficient for the preparation of arylpotassium trifluoroborates (Scheme 5).



**Scheme 5**

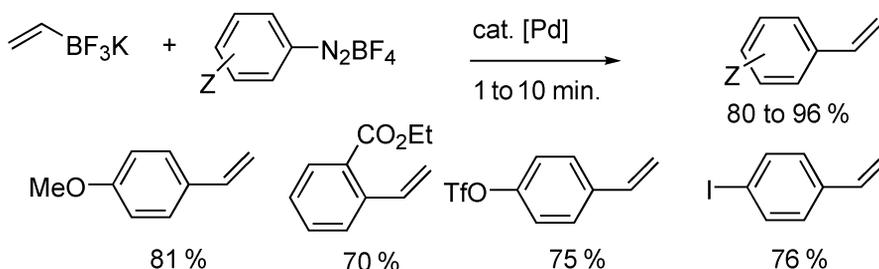
More particularly, this procedure proved to be general and applied for the preparation of potassium alkynyltrifluoroborates from terminal and potassium alkenyltrifluoroborates from lithium or magnesium derivatives. For example, simple potassium vinyltrifluoroborate **10** was prepared on a large scale and with high yields up to 85 %, from vinylmagnesium chloride, by treatment with trimethoxyborane followed by in situ addition of  $\text{KHF}_2$  (Scheme 6). All those alkenyl- and alkynyltrifluoroborate salts proved to be highly stable for several years at room temperature, which is not the case for the trivalent alkenylboron compounds [23].



**Scheme 6**

## POTASSIUM ORGANOTRIFLUOROBORATES IN Pd-CATALYZED REACTIONS

In 1997, Darses and Genêt were the first to show that potassium aryltrifluoroborates were suitable substrates in Pd-catalyzed reactions. More particularly, potassium vinyltrifluoroborate proved to be a highly efficient vinylating agent of diazonium salts [22b]. Indeed, Pd-catalyzed cross-coupling reaction of arenediazonium tetrafluoroborates with potassium vinyltrifluoroborates afforded styrene derivatives as the sole products in good yields at room temperature (Scheme 7).

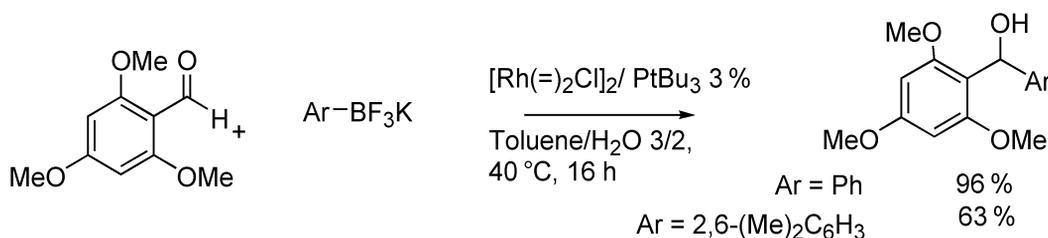


Scheme 7

It is important to note that the cross-coupling reaction with vinylboronate esters was not selective, giving mixtures of compounds arising from SM and Heck reactions in all cases [23]. In 2000, Scalone and coworkers, at Hofmann-La Roche, described the introduction of a vinyl substituent on pyrimidine derivatives using potassium trifluoro(vinyl)borate. Reaction conditions were optimized, and it was found that  $\text{PdCl}_2(\text{dppf})$  showed the highest activity, and the highest conversions and purities were achieved in alcoholic solvents [24]. Of importance is that this reaction could be conducted on a kilogram scale. These conditions proved to be quite general for the introduction of an alkenyl moiety on aryl halides or pseudo-halides and used by Molander and others [19–21].

### POTASSIUM ORGANOTRIFLUOROBORATES IN Rh-CATALYZED REACTIONS

The 1,2- and 1,4-additions of organometallic reagents to unsaturated compounds are some of the most versatile reactions in organic synthesis. In that context, it has been shown that trivalent organoboronic acids add efficiently to unsaturated substrates in the presence of Rh catalyst [25]; potassium trifluoro(organo)borates also participate in Rh-catalyzed addition reactions [26] to electron-deficient aldehydes. We have developed a more efficient system using Rh catalyst  $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$  (3 mol %),  $\text{P}(\text{tBu})_3$  (3 mol %). In the presence of an electron-rich phosphine such as  $\text{PBu}_3$  and water (toluene/ $\text{H}_2\text{O}$ ), the reaction proved to be general, allowing the production of highly hindered diaryl carbinols (Scheme 8), and aliphatic aldehydes were also reactive under these conditions [27].



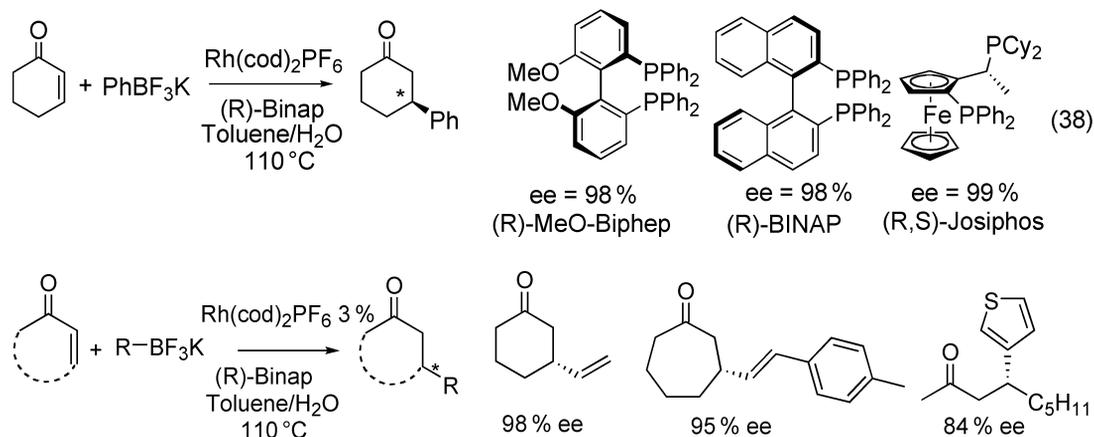
Scheme 8

Interestingly, in the absence of water, a direct access to ketones from aldehydes via Rh-catalyzed cross-coupling reaction with potassium trifluoro(organo)borates was readily achieved [28].

### ASYMMETRIC 1,4-ADDITION TO MICHAEL ACCEPTORS

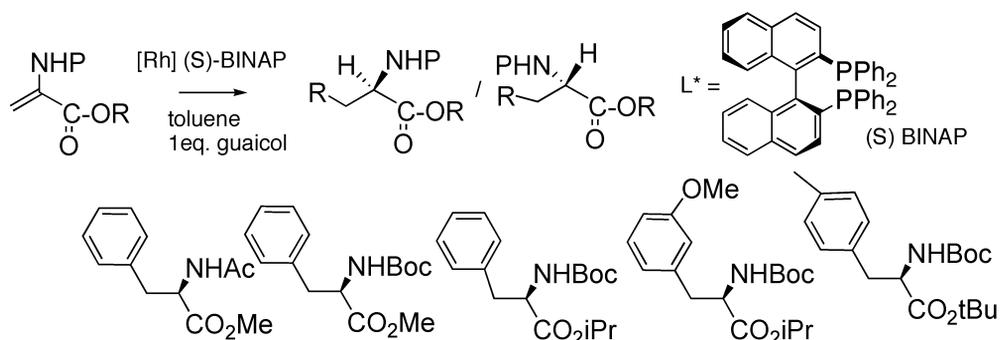
Hayashi and Miyaura have independently reported 1,4-addition of boronic acids to Michael acceptors using  $\text{Rh}(\text{acac})_2\text{C}_2\text{H}_4$  in the presence of BINAP [29]. Batey et al. have reported the first achiral conjugate addition of potassium trifluoro(organo)borates to enones [26]. However, the asymmetric 1,4-addition turned out to be trickier than the racemic version. Most Rh catalysts described earlier by Batey,

Miyaura, and Hayashi underwent poor conversions and/or low ee. We have reported, after careful optimization of the reaction system including ligand, solvent, and temperature, that  $[\text{Rh}(\text{cod})_2]\text{PF}_6$  associated to chiral phosphine BINAP, JOSIPHOS, and MeO-BIPHEP was a highly efficient system. The presence of water is also crucial for this reaction: in its absence, the reaction and the asymmetric induction were very slow. On the other hand, an excess of water slows down the reaction and in pure water no asymmetric induction was observed. A controlled amount of water compared to boron reagent is required, typically 10:1 mixture of toluene/water [30]. Potassium trifluoro(organo)borates react efficiently and selectively to enones (Scheme 9). The reaction has been applied to  $\alpha,\beta$ -unsaturated amides, esters, and lactones [31].



**Scheme 9**

Miyaura et al. have reported the 1,4-addition reactions of potassium trifluoro(organo)borates to Michael acceptor using dicationic Pd catalyst [32]. The tandem 1,4-addition-enantioselective protonation of N-protected amidoacrylates would provide a new and efficient route to enantiomerically enriched  $\alpha$ -amino acids. When we started our studies, only one example was described by Reetz using catalytic asymmetric 1,4-addition of phenyl boronic acid to methyl  $\alpha$ -acetamido acrylate with binol diphosphinite ligand and furnished the phenylalanine in 77 % ee [33]. Using potassium aryltrifluoroborates in the presence of water, the ee values were usually below 28 %. However, we have shown that the use of the nontoxic 2-methoxyphenol or guaiacol as proton source instead of water could control the  $\alpha$  chiral center. The conjugate addition of potassium aryl- and alkenyltrifluoroborates to N-acylamidoacrylates mediated by a chiral Rh complex in the presence of 1 equiv of guaiacol furnishes a variety of  $\alpha$ -amino acid derivatives with good enantioselectivities up to 89.5 % ee using Rh-BINAP catalyst [34]. With the optimal conditions in hands, we evaluated the scope and limitations of this tandem 1,4-addition-enantioselective protonation. Several N-protected dehydroamino methyl esters were tested, N-acetyl and N-Boc protecting groups gave good yield and selectivity. The influence of steric hindrance from methyl to isopropyl and *t*-butyl ester improved the enantioselectivity ee up to 95 % [35]. However, lower yields were generally achieved using *t*-butyl ester; a good compromise is the use of isopropyl ester (Scheme 10).

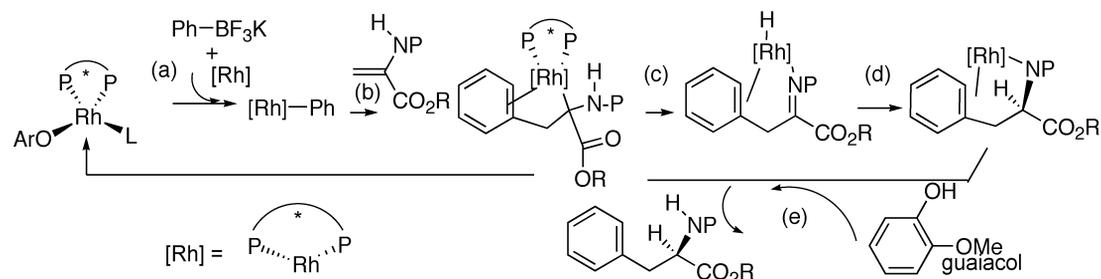


(S) BINAP e.e.89.5%; Yld 89% e.e. 89.5%; yld 82 % e.e. 93 %; yld 76 % e.e 92 %; yld 72 % e.e. 95 %; yld 60 %

Scheme 10

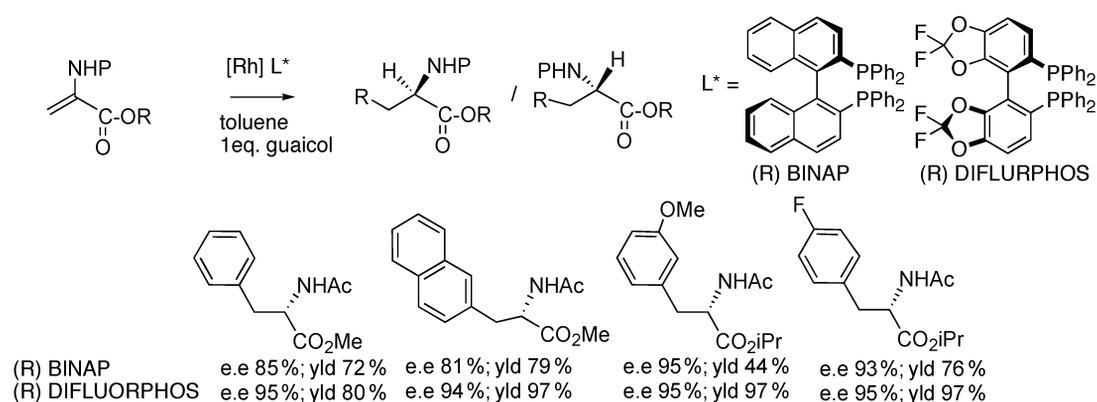
### REACTION PATHWAY OF THE TANDEM 1,4-ENANTIOSELECTIVE Rh-CATALYZED REACTION

Initially, we believed that this reaction proceeded through an oxa  $\pi$ -allyl Rh intermediate as established by Hayashi [29c]. Actually, it appears that the presence of a free N–H bond in  $\alpha$  position to the Michael acceptor was essential in order to achieve a high level of enantioselectivity. Deuterium labeling studies show new interesting aspects of this Rh-catalyzed 1,4-addition. The catalyst cycle involves (a) transmetalation of the aryl group from boron to Rh; (b) insertion of the olefin into the aryl-Rh bond, forming a Rh alkyl species; (c)  $\beta$ -elimination giving a Rh-imino complex; (d) 1,3 hydrogen shift from Rh to carbon, forming the Rh-NP intermediate; and (e) its cleavage with guaiacol giving the addition product and aryloxo Rh species (Scheme 11) [36].



Scheme 11

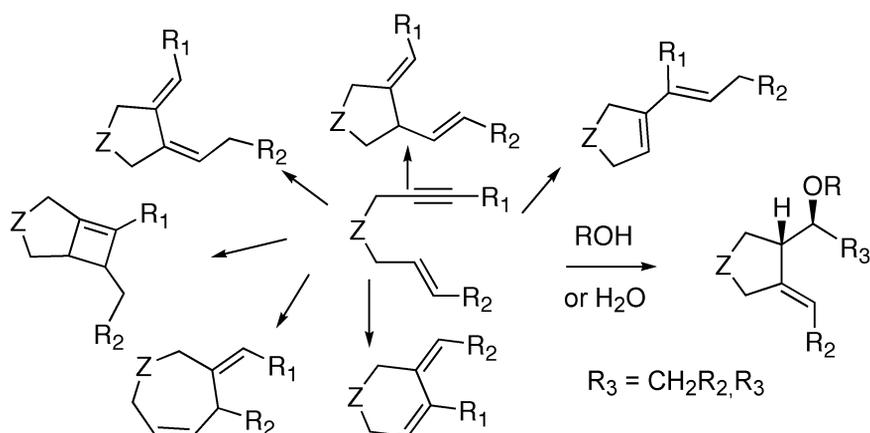
The potential energy profiles have been studied by density functional theory (DFT) calculations. The computed sequence of the elementary steps, relative intermediates, and transition states agrees with the previous proposal step (c), which is endothermic with an energy barrier of 27.8 kcal mol<sup>-1</sup> [36]. This step is the rate-determining step. Thus, we anticipated that a more  $\pi$  acceptor than BINAP should facilitate the  $\gamma$ -elimination and improve the selectivity, having developed DIFLUORPHOS, which is an original atropisomeric ligand with original steric and electronic properties [36]. We were pleased to find that under optimized conditions both yields and enantioselectivities were significantly increased using Rh-DIFLUORPHOS catalyst (Scheme 12) [37].



Scheme 12

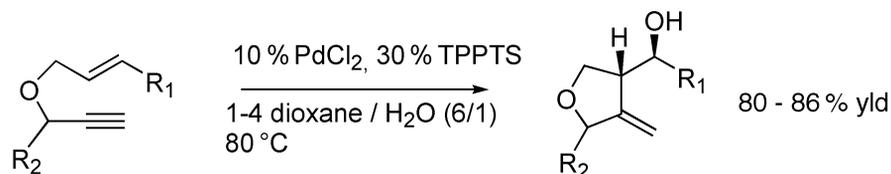
### REORGANIZATION OF 1,6-ENYNS WITH Pd AND Pt IN WATER

Activation of alkynes with transition-metal salts (Pd, Pt, Au) allows their reactions with alkenes, giving rise to a myriad of interesting processes like cyclizations. Weak nucleophiles such as alcohols and water can also participate in these processes, giving rise to alkoxy and hydroxy compounds (Scheme 13) [38].



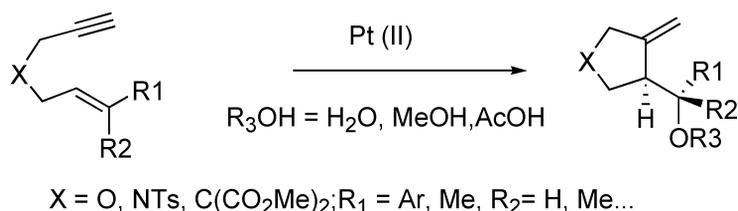
Scheme 13 Cyclization reactions of enynes catalyzed by transition metals.

Actually, this reaction was discovered 10 years ago in our group in the cycloisomerization 1,6-enynes using Pd(OAc)<sub>2</sub>-TPPTS as catalyst. The cyclization proceeds diastereoselectively with simultaneous formation of C–C and C–O bonds via hydroxy functionalization (Scheme 14) [39].



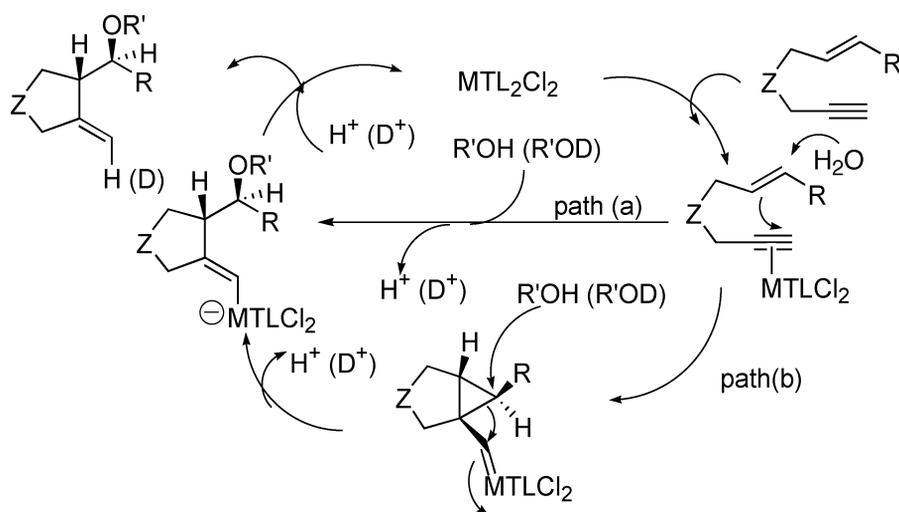
Scheme 14

In 2000, Echavarren et al. found that Pt(II) catalysts are highly efficient in this cyclization reaction. The addition of water, alcohols, and acetic acid led to the formation of a wide range of functionalized hetero- and carbocycles (Scheme 15) [40].



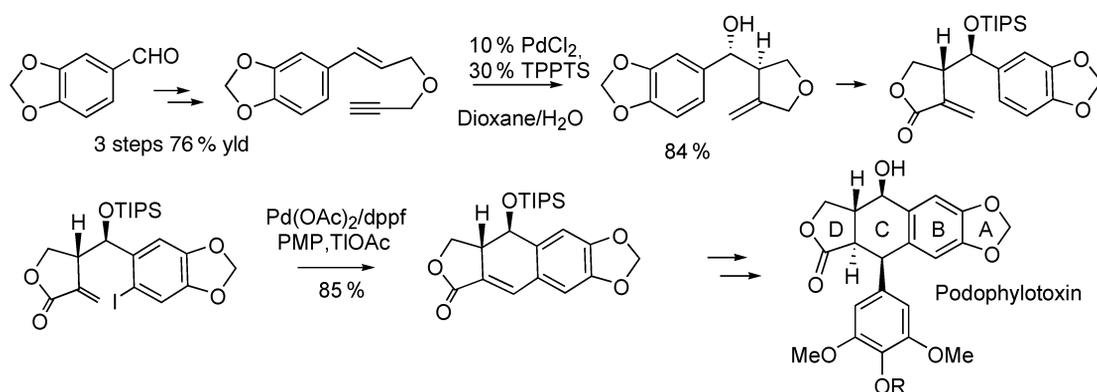
**Scheme 15**

Taking into account deuterium labeling studies, the reaction is believed to proceed via two competitive pathways. Apparently, the Pd(II) and Pt(II) reactions are closely related reactions. Complexation of the enyne by Mt(II) catalysts promotes intramolecular anti addition followed by concomitant attack of water or alcohol similar to Wacker process pathway (a). An alternative pathway (b) could be the intramolecular reaction of the alkene to form a cyclopropyl Mt-carbene intermediate; subsequent attack of nucleophile (methanol or water) at the cyclopropyl carbon would give rise to the formation of a five-membered intermediate which undergoes subsequent protodemetalation (Scheme 16) [41,42]. The hydroxy and alkoxy cyclization reactions were developed with various 1,6-enynes in the presence of Pd and Pt catalysts. We investigated the asymmetric version of this novel and ideal reaction in terms of atom economy and reported the first enantioselective Pt-promoted enyne carbo-alkoxy-cyclization. The use of silver salts combined with (*R*)-Ph-BINEPINE, an atropisomeric monophosphane ligand, was found to be the best combination, giving enantioselectivity up to 85 % ee [43].



**Scheme 16** Mechanism of Pt and Pd hydroxy and alkoxy cyclizations.

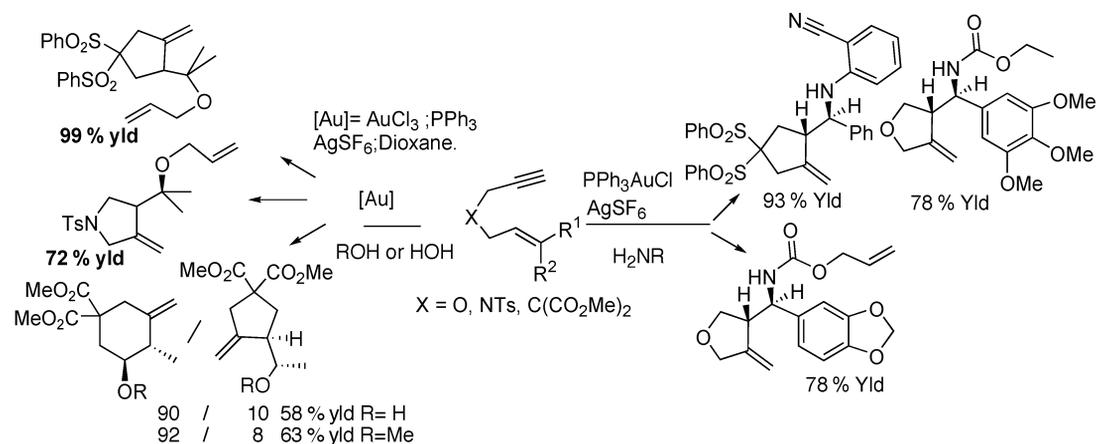
This atom-economical reaction has been applied to the synthesis of antitumor podophylotoxin precursors (Scheme 17).



**Scheme 17** Synthesis of a podophylotoxin intermediate.

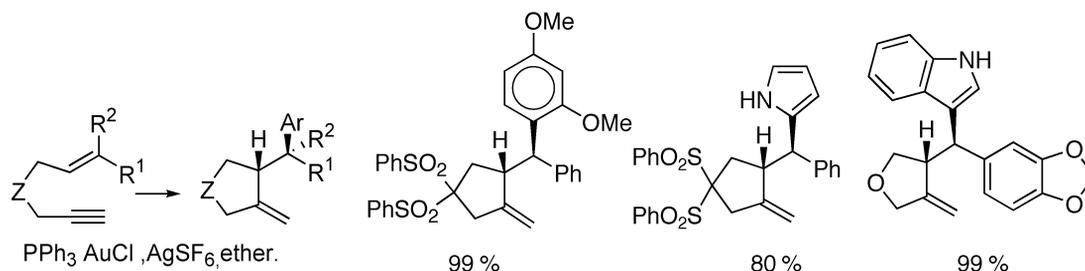
## REORGANIZATION OF ENYNES WITH Au CATALYSTS

The recent acceleration in research activity in the field of Au catalysis is due to its high affinity for alkynes, arenes, allenes, and even alkenes. Whilst Au was considered an expensive metal, it is in fact less expensive than Pt and Rh complexes that are commonly used for standard manipulations, including large-scale industrial applications. Au catalysis represents a new frontier in catalysis and was highlighted in recent reviews [45]. In pursuit of our investigation of metal-catalyzed cycloisomerization of enynes, we envisaged using Au. After optimization, we found that the combination of AuCl<sub>3</sub> (10 mol %), PPh<sub>3</sub> (10 mol %), and silver salt (AgSF<sub>6</sub>) in dioxane 24 at room temperature promoted efficiently the tandem hydroxy- or alkoxy cyclization of enynes. The reaction led to carbo- and heterocyclic alcohols and ethers in good to excellent yields (Scheme 18) [46]. The hydroamination/cycloisomerization of 1,6-enynes catalyzed by Au also leads to the corresponding heterocyclic amino derivatives. For the high chemical yields in this reaction, PPh<sub>3</sub>AuCl must be used in combination with AgSF<sub>6</sub> in tetrahydrofuran (THF) or dioxane at room temperature. The addition of carbamates and primary aromatic amines provides particularly good nucleophiles, and the corresponding cyclized compounds are formed in good to excellent yields (Scheme 18) [47].



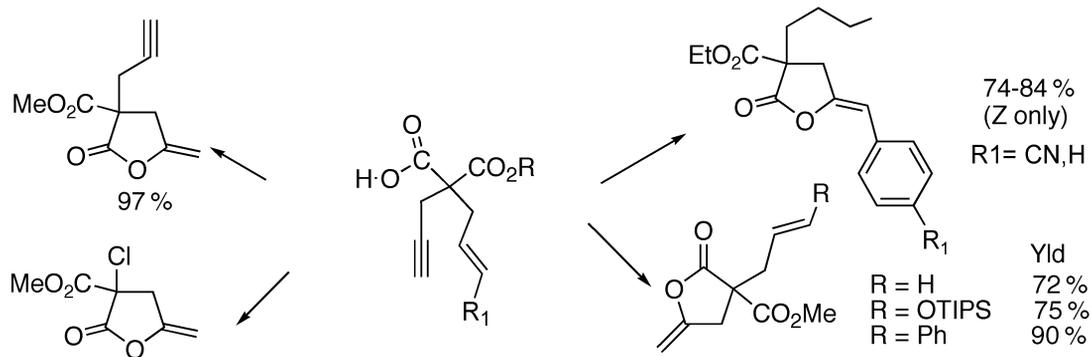
**Scheme 18** Hydroxy, alkoxy, and amino cyclization of enynes with Au catalysts.

This reaction is not restricted to water, alcohols, and amines. Electron-rich arenes and hetero-aromatic derivatives using  $\text{PPh}_3\text{AuCl}$  (3 mol %) and silver salt  $\text{AgSF}_6$  (3 mol %) readily reacted in ether, giving a wide range of functionalized cyclic compounds. This tandem Friedel–Craft-type addition proceeded diastereoselectively (Scheme 19). Then, considering the mechanism with Au catalysts, the cyclization step may proceed by stereoselective attack of the nucleophile on the transient carbene Au species path b (Scheme 16) [42].



**Scheme 19** Tandem Friedel–Crafts addition carbocyclization of functionalized enynes.

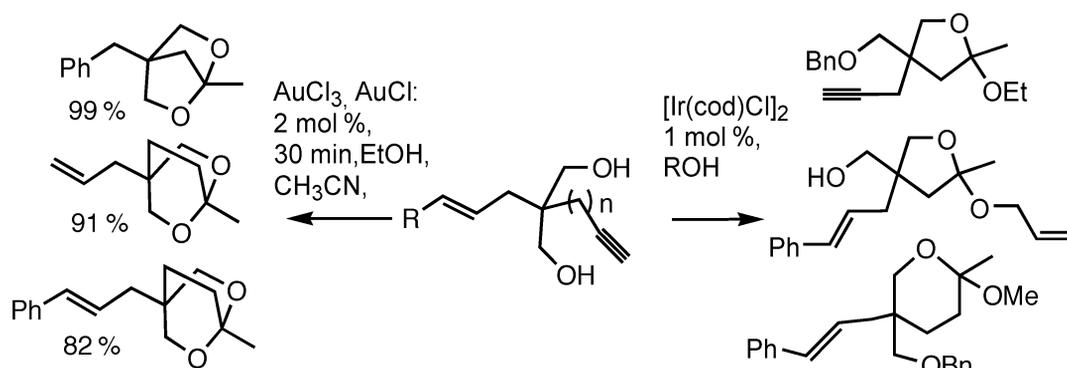
We also have demonstrated that functionalized acetylenic acids may be cyclized under extremely mild conditions at room temperature. A wide range of functionalized acetylenic acids reacted at room temperature in the presence of 5 % of Au(I) in acetonitrile giving the corresponding lactones in good yield [49]. The cyclization proceeded smoothly within 2 h under a 5-exo mode. Carboxylic acids containing internal alkyne were also cyclized in the presence of 5 % of Au chloride, affording exclusively the  $\gamma$ -lactone with Z stereochemistry. This stereochemistry supports a mechanism, implying anti intramolecular addition of carboxylic acid to a Au-alkyne intermediate resulting from an initial activation of the triple bond (Scheme 20). Interestingly, the chemical yields of this Au intramolecular addition of carboxylic acid are good even in the presence of a styrenyl or allyl side chain.



**Scheme 20** Cyclization of acetylenic acids with Au(I) catalysts.

Teles reported the nucleophilic intermolecular addition of alcohols to alkynes with cationic Au complexes, Hashmi and coworkers first demonstrated that ethynyl allyl alcohols can efficiently cyclize to furans [45]. We had reported a tandem cycloisomerization/hydroalkoxylation of bis-homopropargylic alcohols at room temperature, giving functionalized furanyl and pyranyl building blocks in the presence of Ir complexes [50]. In contrast with the Ir-catalyzed reaction, we have found that either Au(I) or Au(III) catalysts promoted cycloisomerization of bis-homopropargyl diols under very mild conditions

at room temperature within 30 min, leading to the functionalized strained bicyclic ketals [51]. Under these conditions, the substrates containing allyl or styrenyl do not react (Scheme 21).



**Scheme 21** Cycloisomerization of homopropargylic alcohols with Ir and Au catalysts.

Using an unsymmetrical triol containing one secondary and two primary hydroxyl groups, the spirocyclization occurred chemoselectively by both primary alcohols, giving the bicyclo (3.2.1) ketal in 74 % yields. An elegant application of this Au spirocyclization has been reported by Forsyth and co-workers for the synthesis of A-D ring of azaspiracid, a marine toxin [52].

## CONCLUSION

A water medium can promote various old and new reactions using a wide variety of transition-metal complexes (Pd, Pt, Rh, Au). The transition-metal-catalyzed reactions with water-soluble phosphanes provide advantages of a two-phase aqueous system, easy separation, and recycling the expensive metal and ligand. Some reactions are unprecedented in water; the presence of water is crucial in some reactions for C–C and C–X bond formations, since some substrates do not react under anhydrous conditions. We have developed ideal atom-economical reactions leading to highly functionalized carbo- and heterocycles. The use of Au catalysts promotes highly efficient reorganization of enynes to a wide range of cyclic derivatives under very mild conditions. These reactions would allow further applications to the synthesis of biologically active compounds.

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