New Wind in Old Sails: Novel Applications of Triphos-based Transition Metal Complexes as Homogeneous Catalysts for Small Molecules and Renewables Activation

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Dedicated to Prof. Manfred Scheer on the occasion of his 60th birthday.

Abstract: Recent developments in the coordination chemistry and applications of Ru-triphos [triphos = 1,1,1-tris-(diphenylphosphinomethyl)ethane] systems are reviewed, highlighting their role as active and selective homogeneous catalysts for small molecule activation, biomass conversions and in carbon dioxide utilization-related processes.

Keywords: Biomass · Carbon dioxide utilization (CDU) · Homogeneous catalysis · Ruthenium · Triphos

Introduction

Polydentate phosphines are nowadays recognized as one of the most important classes of ligands having widespread applications in coordination chemistry. The facially coordinating tridentate ligand triphos [triphos = 1,1,1-tris-(diphenylphosphinomethyl)ethane] and its derivatives have been investigated in detail, due to their ability to yield a large variety of transition-metal complexes, many of which have found application in catalysis.1

Bianchini and co-workers described the use of triphos in transition-metal catalysis using platinum group metals for hydrogenation and hydroformylation of alkenes,2 hydrogenation of N-heterocycles,3 hydrogenation, hydrolysis, and oxidation of thiophene,4 and its derivatives have been investigated in detail, due to their ability to yield a large variety of transition-metal complexes, many of which have found application in catalysis.4

In particular, the reactivity of ruthenium(II)-triphos complexes toward various substrates in hydrogenation reactions5,6 were studied extensively by NMR and IR spectroscopies.7 The increased stability provided by the tripodal nature of the triphos ligand promotes the highly active catalyst formation for the hydrogenation of esters, amides, and even free carboxylic acids.8 Elsevier and co-workers reported in 1997 the hydrogenation of activated esters using in situ formed catalysts obtained from ruthenium precursors such as [Ru(acac)3] and triphos.9,10

Since then, several research groups have investigated the mechanism of hydrogenation in an attempt to explain the role of the hydride complex in these reactions. Frediani and co-workers studied the mechanism of hydrogenation of esters and lactones by a deuterium labeling study.9 Chaplin and Dyson proposed a mechanism for the hydrogenation of alkenes using a Ru/triphos complex involving non-classical hydrides.10

In recent years the use of ruthenium-triphos catalytic systems, both as well-defined complexes and as in situ combinations of metal precursors and ligand have been employed in new and old reactions such as the catalytic conversion of biomass11 and CO2 utilization for the production of fuels and chemicals.12

Selective Catalytic Conversions of Biomass Feedstocks to Useful Chemicals

In view of the changing world energy demands, biomass could potentially become an important resource for the production of biofuels, bioenergy and biomaterials. Feedstocks derived from biomass are generally subdivided in three classes: starchy feedstocks, triglyceride feedstocks, and lignocellulose. The latter is the most abundant class of biomass and its carbohydrates can be used to produce building block chemicals via biological or chemical means, which in turn can be used to obtain a number of high-value products. Usually, the main target for building block chemicals is the presence of functional groups that can be transformed into new useful molecules.13

The development of new synthetic methods and highly specific catalysts is therefore required for the functionalization of bio-substrates to obtain a broad range of chemical compounds in a sustainable way.

Among the building blocks that can be produced from sugars, levulinic acid (LA) and itaconic acid (IA) possess a central importance within the biorefinery. Levulinic acid has frequently been used for the conversion of γ-valerolactone (GVL), a cyclic ester considered as one of the key components in the biorefinery. A further conversion of LA can be undertaken to obtain biogenic diols, such as 1,4-PDO, and the cyclic ether 2-methyltetrahydrofuran
(2-MTHF) useful as monomer for biodegradable polymeric materials and as an alternative solvent in the pharmaceutical industry, respectively (Scheme 1). Itaconic acid is also an important feedstock and its reactivity is reminiscent of maleic acid and maleic anhydride, still obtained from petrochemical sources.

Recently, Leitner and co-workers reported the use of the multifunctional catalyst system composed of the ruthenium precursor Ru(acac)₃ and triphos with ionic and/or acidic additives for selective conversions of levulinic acid (LA, Scheme 2) and itaconic acid (IA, Scheme 3) to lactones, diols and cyclic esters via hydrogenation-dehydration sequences.\(^{1,14,15}\)

In the latter publication, it was shown that a fundamental role was played by the combination of the stereoelectronic properties of the ligand, the effect of ionic additives on the reactivity and stability of the active species, the strength of the acidic additive, reaction temperature and pressure. In the presence of a Ru(acac)₃/triphos ratio of 1:2, LA and IA were converted into the desired products with over 90% yields, at 160 and 195 °C respectively, under a hydrogen pressure of 100 bar with control of the dehydration process due to the acidity of the reaction medium (Schemes 2 and 3).\(^{14}\)

Leitner and co-workers also reported a combined theoretical and experimental study to explain the mechanism of this system.\(^{15}\) All obtained results suggest that the complex fragment [RuH(triphos)]\(^+\) represents the catalytically active species for the reduction of the C=O functionality in aldehydes, ketones, lactones, and even free carboxylic acids. DFT calculations suggest that the reaction involves a hydride transfer from Ru–H onto the carbonyl or carboxyl group followed by protonation of the resulting Ru–O unit via σ-bond metathesis from a coordinated dihydrogen molecule, regenerating the catalytically active Ru–H species.

A significant step forward in the synthetic chemistry of Ru-triphos complexes was described by Leitner and co-workers, reporting the novel \([\text{Ru(P)}(\text{TMM})]_\text{L}\) complex (TMM = trimethylenemethane), synthesized from \([\text{Ru(cod)}(\text{methallyl})]_\text{L}\) (cod= 1,5-cyclooctadiene, methallyl = \(\eta^1\)-C₅H₅) and tripodal phosphine ligands P, (Scheme 4). These complexes were found to be active catalysts for hydrogen transfer reactions and C=O cleavage of \(\beta\)-[O]-4'-glycerolarylether linkages of lignin.\(^{16}\)

The experiments were carried out using 2-phenoxyl-1-phenylethanol as the model compound for lignin linkages and comparing the activity of catalyst bearing mono (PPh₃) and bidentate phosphines (dppe) and \(9,9'\text{-dimethyl-9H-xanthene-4,5-diyl} \) bis(diphenylphosphine) (A) to the tri-
podal phosphines 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos-B), and bis(diphenylphosphinoethyl)phenylphosphine (triphos-C). (Scheme 5).

The catalysts formed in situ from [Ru(cod)(methallyl)] and phosphine ligands. More recently, Beller and co-workers performed in the presence of Ru(acac)3 as metal precursor and p-toluenesulfonic acid (PTSA) as an additive in catalytic amounts, obtaining low yields of GVL. Therefore, various phosphines (Scheme 7) were added to the reaction mixtures and three different triphos analogues (L3, L4, L6) have demonstrated high efficiency, especially L6, leading to the highest yields (95%), catalyst turnover numbers (TON = 75855) and catalyst turnover frequencies (TOF = 1382 h⁻¹).

![Fig. 1. X-ray crystal structure of complex [Ru(triphos)(TMM)] (TMM = trimethylenemethane).][16]

**Production of Chemicals and Fuels from Small Molecule Activation**

Other applications of the ruthenium/triphos catalytic system were found in the activation of small molecules such as CO, and H2, and in the reduction of unsaturated functional groups in more complex organic substrates to obtain important classes of compounds both in bulk chemistry and as high-value intermediates in organic synthesis.

**Amines**, an important class of compounds finding application in many industrial processes,[9f] can in principle be obtained from the hydrogenation of amides with molecular hydrogen, allowing for their more sustainable production in the pharmaceutical industry.[19] In the past, this reaction was reported using ruthenium/triphos but a mixture of products was obtained without formation of the desired primary amines.[20]

Cole-Hamilton and co-workers proposed the use of the same system but in the presence of water and ammonia, fundamental requirements for the stabilization of the catalyst and for the selective primary amine formation, respectively.[19] The best results were obtained using [Ru(acac)3] and triphos in the presence of liquid ammonia with a conversion of 100% and a selectivity to primary amine of 44%. The selectivity was increased to 85% using aqueous ammonia. A mechanism was proposed for this reaction (Scheme 8).

More recently, the same authors reported on the hydrogenation of amides to primary, secondary and tertiary amines with high selectivity in the presence of [Ru(acac)3], triphos and methanesulfonic acid (MSA). With this catalytic system, the hydrogenation of amides to amines in the presence of aromatic rings was also performed without cleavage of the C=N bond, which is the principle cause of the alcohols and other byproducts formation (Scheme 9). [21]

At hydrogen pressure of 10 bar and temperature around 200–210 °C, the catalysis activated in situ from [Ru(triphos-C)(TMM)] at 135 °C, yields of over 90% of phenol and acetophenone were achieved after only 2 h (Scheme 6). The complexes [Ru(triphos-B)(TMM)] and [Ru(triphos-C)(TMM)] were also characterized in the solid state by single crystal X-ray diffraction (Fig. 1).

More recently, Beller and co-workers investigated the conversion of LA to GVL using ruthenium–triphos based systems as efficient catalysts at 140 °C under solvent-free conditions.[17]

Initially, methyl levulinate was used as the model substrate and the reaction was performed in the presence of Ru(acac)3 as metal precursor and p-toluenesulfonic acid (PTSA) as an additive in catalytic amounts, obtaining low yields of GVL. Therefore, various phosphines (Scheme 7) were added to the reaction mixtures and three different triphos analogues (L3, L4, L6) have demonstrated high efficiency, especially L6, leading to the highest yields (95%), catalyst turnover numbers (TON = 75855) and catalyst turnover frequencies (TOF = 1382 h⁻¹).

![Scheme 4. Formation of complexes [Ru(P surrogate ligand) and the tridentate phosphines P3 = B, C.[16]](https://example.com/scheme4)

![Scheme 5. Cleavage of 2-phenoxystyrene using [Ru(cod)(methallyl)] and phosphine ligands.[16]](https://example.com/scheme5)

![Scheme 6. Temperature effect on the catalytic cleavage of 2-phenoxystyrene using [Ru(cod)(methallyl)] and triphos-C.[16]](https://example.com/scheme6)
The best results were obtained for benzylimide and N-phenylacetamide with a conversion of 100% and selectivity up to 90%.

The role of the so-formed mixture of Ru-triphos-MSA complexes would act as reservoir for the [Ru(triphos)]^+ fragment, identified as the active catalytic species, and tune the protonation-deprotonation steps necessary for efficient catalyst turnover.[21]

The complex [Ru(triphos)(TMM)] found various applications as an efficient homogeneous catalyst, beyond the C=O bond cleavage in lignin model compounds discussed above.[17] It was tested for the hydrogenation of formate esters and CO₂ hydrogenation to methanol.

Leitner and co-workers demonstrated that this system is a useful catalyst for the hydrogenation of a wide range of challenging functionalities such as carboxylic esters, amides, carboxylic acids, carbonates, and urea derivatives.[23] From the combination of multinuclear NMR spectroscopic studies and DFT calculations, it was shown that the active species is the [Ru(triphos)(solvent)]^+ complex (solvent = THF, CH₂CN) obtained by reaction of [Ru(triphos)(TMM)] with H₂ either under neutral conditions or in the presence of catalytic amounts of an acid such as methansulfonic acid (MSA) or HNTf₂ (bis-trifluoromethane sulfonamide) as additive.[22]

DFT calculations demonstrated together with experimental results that the use of complex [Ru(triphos)(TMM)] as hydrogenation precatalyst without further additives enables the selective reduction of C=O bonds in carboxylic esters, acids, anhydrides, and selected amides (Scheme 10). By adding an acidic co-catalyst such as HNTf₂ to the reaction mixture under hydrogen pressure (pH₂ = 50 bar), the cationic species [Ru(triphos)(Solvent)(H)(η²-H₂)]⁺ is formed instead, a selective catalyst for the reduction of primary amides, ureas, and carbonates with excellent yields. The presence of a co-catalyst is needed to avoid the formation of the catalytically inactive complex [Ru(triphos)(CO)(H)₂]⁺, a thermodynamic sink connected to catalyst deactivation pathway.

Another important class of molecules are methyl-substituted amines, a class of bioactive compounds utilized as intermediates for chemical syntheses.[23] Novel protocols for sustainable amine methylation methods are very attractive. Currently, the industrial method for methylation of amines uses toxic solvents and methylation reagents such as MeI, MeOTf etc.[24] In the past years, several research groups have focused their attention on catalytic methylations using CO₂ and H₂, a sustainable method with H₂O as the only by-product (Scheme 11).

Beller and co-workers reported the use of the CO₂/H₂ mixture as the methylation reagent using [Ru(acac)₃] and triphos in the presence of a catalytic amount of a
Brønsted acid as the most active protocol for the methylation of both aromatic and aliphatic amines. Under these conditions, a reaction pathway was proposed that proceeds via formamide and methanol intermediates (Scheme 12).

Leitner and coworkers studied the chemoselectivity of [Ru(triphos)(TMM)] catalyst in coupling reactions of primary amines, aldehydes, and CO₂ to produce tertiary N-methyl amines in one step[26] (Scheme 13).

Initially, the reaction conditions were optimized starting with the methylation of amines in the presence of HNTf₂ as co-catalyst. As shown in Scheme 14, an increase of temperature and reaction time favored the formation of the methylation vs. the hydrogenation product.

The enhanced selectivity is due to the use of non-coordinating anion HNTf₂, different from MSA. After investigating a set of different isolated imines, the reaction was carried out coupling directly primary amines, aldehydes, and CO₂. Also in this case, a range of unsymmetrical tertiary amines were synthesized in excellent yields.[26] Finally, the reductive methylation of the imine group in N-methyl amine for the synthesis of butenafine, an antifungal agent, was carried out to test the scope of this method in a commercially relevant process (Scheme 15).

Cantat and co-workers recently reported the use of formic acid (FA) as carbon and hydrogen source for methylation of amines, expanding on their previous reports on this kind of reaction using hydroxilanes as sacrificial reductants. The reactions were carried out at 150 °C using a combination of [Ru(COD)(methylallyl)] precursor and triphos as catalyst, in the presence of HCOOH and MSA, achieving a good conversion of aniline to N-methyl aniline (major product) and N,N-dimethylaniline.[27]

Increasing the HCOOH loading up to an optimal value of 6 equivalents, the formation of N-Ch₃ derivatives was favored and the yields of N-methylaniline and N,N-dimethylaniline increased. The presence of an acid co-catalyst is crucial to guarantee the catalytic activity. In particular, for the methylation of secondary amines HNTf₂ was found to be the most efficient additive (Scheme 16).

However, the limits of the methylation reaction with HCOOH emerged from the study with a wide variety of amines, complemented by DFT calculations.[23] The N–CH₃ group formation proceeds via formylation/transfer hydrogenation with metal hydride intermediate as rate determining step, occurring under thermodynamic control.

Ru/triphos catalytic systems involving CO₂ and H₂ activation have also been used for the direct synthesis of formic acid and formate or methanol. These simple organic molecules are rich in hydrogen content and can in turn be used as Liquid Organic Hydride Carriers (LOHC) to generate H₂ by catalytic dehydrogenation reactions.

Recently, our group investigated the HCOOH dehydrogenation reaction using both the Ru(acac)/triphos in situ system and the isolated complex [Ru(triphos)(MeCN)](OTf)₂ as promising homogeneous catalysts for this reaction.[25] In particular, [Ru(triphos)(MeCN)](OTf)₂ showed superior performances with a TON of 10000 after 6 h using 0.01 mol% of the catalyst and allowed for recycling up to eight times (0.1 mol% catalyst) giving a total TON of 8000 after ca. 14 h of con-
Continuous reaction at 80 °C in the presence of OctNMe₂ (Fig. 2).

Mechanistic details on the reactivity of complex [Ru(triphos)(MeCN)](OTf) with formate and formic acid/ammonia were obtained by a combination of variable temperature (VT) NMR experiments and DFT calculations. It was shown that ligand substitution led to precatalyst activation giving a bis-formate complex [Ru(triphos)(η²-O₂,CH)(η²-O₂,CH)] which then proceeds to release H₂ and CO₂.

Cantat and coworkers reported the efficient synthesis of methanol by direct disproportionation of formic acid using [Ru(triphos)(TMM)] as catalyst. The reaction was carried out in THF at 150 °C in the presence of methanesulfonic acid (MSA) reaching methanol yields of up to 50.2 %. A combination of NMR studies and DFT calculations was carried out to investigate the competition between the dehydrogenation of formic acid and its disproportionation to MeOH. DFT calculations highlighted the central role of the hydride complex [Ru(κ²-triphos)(η²-O₂,CH)] derived from [Ru(κ²-triphos)(η²-O₂,CH)] (η²-O₂,CH) by CO₂ elimination and hydride transfer (triphos = simplified triphos model, Me instead of Ph groups on P atoms), representing the rate-determining step of the reaction. Coordination of FA followed along different pathways, leading to dehydrogenation vs. disproportionation (Scheme 17).

Methanol can also be obtained by steering the selectivity of CO₂ hydrogenation with suitable catalysts and reaction conditions. Such a process would represent an important example of CDU (carbon dioxide utilization) and allow for the sustainable use of waste greenhouse gas into a valuable feedstock. Leitner showed that both the in situ generated Ru(acac)/triphos system and the ruthenium complex [Ru(triphos)(TMM)] are active in the homogeneous hydrogenation of CO₂ to methanol, at 140 °C under a total CO₂/H₂ (1:3) pressure of 80 bar under acidic conditions (Scheme 18).

Mechanistic studies obtained from NMR experiments and DFT calculations demonstrated that the cationic formate complex [Ru(triphos)(η²-O₂,CH)(solv)]⁺ (solv = THF, CH₂CN) is the catalytically active species, identified by ³¹P NMR signals at 44.2 ppm (room temperature, d₂-THF) that split into a doublet (46.3 ppm, 2P, Jₚₚ = 42.5 Hz) and a triplet (43.9 ppm, 1P, Jₚₚ = 42.5 Hz) at 233 K, further confirmed by [H,³¹P]-HMBC-NMR and [H,³¹C]-HMBC-NMR spectra showing a broad singlet at 8.7 ppm and a singlet at 178.8 ppm, respectively.

DFT calculations were used to explore the mechanism of CO₂ hydrogenation to methanol via the formate complex [Ru(triphos)(η²-O₂,CH)(solv)]⁺ and a catalytic cycle was proposed (Scheme 19).

Furthermore, the catalyst could be recycled in a biphasic system 2-MTHF/H₂O where it was retained in the organic phase while MeOH was extracted within the aqueous phase, opening the possibility for continuous-flow system (Scheme 20).

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**Fig. 2.** Catalyst recycling for HCOOH dehydrogenation reactions in the presence of [Ru(triphos)(MeCN)](OTf) (for conditions see ref. [28]). Reproduced by permission of The Royal Society of Chemistry.
Conclusions

Nowadays, global society needs and economical growth are still dependent on petrochemicals and fossil fuels. Thus, the sustainable production of fuels and chemicals is a topic of great interest.

The use of carbon dioxide as C1 building block has recently attracted interest both for the production of fuels or hydrogen rich molecules (i.e. CO₂ hydrogenation to methanol or formic acid) and the production of important chemicals, contributing to the development of a low-carbon economy. Biomass could potentially become also an important resource for the production of biofuels, bioenergy and biomaterials since the selective de- and refuctionalization of biogenic substrates give important building blocks for the production of high-value chemicals. Both approaches need the development of low-energy routes for activation and/or functionalization of feedstocks, which are often endowed with high chemical inertness. The development and use of highly active and selective catalysts, both homogeneous and heterogeneous, is pivotal to reach this target, as witnessed by the large interest of many research groups in academia and industry around the world.

Among homogeneous catalysts, recently the systems based on ruthenium and the tridentate phosphine triphos, initially known as a good catalyst for hydrogenation of esters, amides, and carboxylic acids, found a new life and use in reactions of new interest including CO₂ and biomass functionalization, showing promising catalytic activity and flexibility. A subtle choice of ancillary ligands is often needed to achieve active and versatile Ru-triphos based molecular platforms. A good example is the choice of TMM (trimethylenemethane) as in complex [Ru(triphos)(TMM)] which found various applications as summarized above.

Received: April 16, 2015
