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Tandem Rhodium Carbonylation Reactions

Philippe Kalck and Martine Urrutigoïty

Abstract This review presents the recent advances in the rhodium-catalyzed tandem carbonylation reactions involving in the main step the hydroformylation. Such reactions open huge opportunities in synthetic chemistry, since they offer a general efficient strategy to synthesize building blocks for fine chemistry, starting from abundant and low price substrates and avoiding the formation of substantial amounts of by-products. This atom-efficient tandem reaction approach shows that rhodium has a privileged place in the CO chemistry, not only to perform the hydroformylation reaction but also to functionalize the aldehyde function in a one-pot process.

Keywords CO chemistry • Rhodium • Tandem reactions involving hydroformylation

Contents

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1 Introduction

Carbon monoxide has been shown to be a powerful building block to functionalize organic products, and the two main organic products obtained by carbonylation are acetic acid (11 million tons per year, 11 MT/y) from methanol [1] and aldehydes by hydroformylation of alkenes (12 MT/y) [2, 3]. The initial hard conditions of catalysis, especially the high pressures required by the cobalt carbonyl complexes, have been replaced by milder conditions due to the development of rhodium complexes whose the coordination sphere is sufficiently sophisticated to reach high reaction rate, chemoselectivity, and regioselectivity. Moreover, the modern recycling processes are efficient enough to avoid the loss of this precious metal and to have industrial units with capacities as high as 500 kT/y.

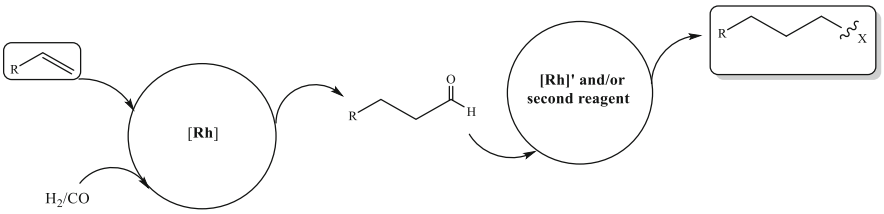
As the major problems in chemical synthesis are the handling of wastes, the search for efficient procedures, and the preservation of resources, many efforts have been devoted to improve the efficiency of the reaction, operating in one sequence, in the absence of isolating the intermediates [4]. This strategy of cascade reactions [5, 6] has been expanded until the synthesis of a given product mimics the principles of biosynthesis, including asymmetric reactions to perform natural product synthesis [7] for advancing the drug discovery and development process [8]. Using tandem (or domino) reactions, two or more bonds are produced, under identical conditions, leading to the formation of more complex molecules in an economic approach, especially since unstable intermediates are immediately transformed [9].

Due to their high reactivity, aldehydes have been also largely used in organic synthesis since they can be easily transformed into alcohols, amines, carboxylic acid derivatives, acetals, etc. The tandem reaction sequences under the hydroformylation reaction conditions have been largely explored in the 1990s, and the Eilbracht's reviews give an interesting view of the performances of the first catalytic systems able to combine hydroformylation reaction and in a second sequence C–H, C–O, C–C bond formations [10, 11].

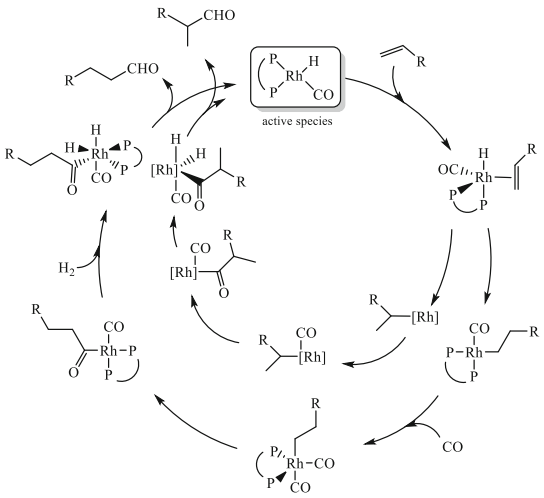
This chapter is devoted to the rhodium-catalyzed tandem carbonylation reactions, involving in the first step the hydroformylation of an alkene. Then, the produced aldehydes are generally transformed in a tandem reaction to yield important chemicals for organic synthesis. A second reagent or a second catalytic cycle operates, starting from the aldehyde as shown in Scheme 1.

1.1 Rhodium-Catalyzed Hydroformylation: Generalities

The hydroformylation reaction of an alkene mainly involves the $[Rh(H)(CO)_2L_2]$ precursor in which L is a phosphorus-containing ligand and more interestingly L_2 a bidentate ligand. Under the reaction conditions, this resting state produces the $[Rh(H)(CO)L_2]$ square-planar active species, which coordinates the alkene substrate ($RCH{=}CH_2$). Transfer of the hydride ligand to one carbon atom of the C=C double



Scheme 1 General feature of the tandem hydroformylation/second functionalization reaction



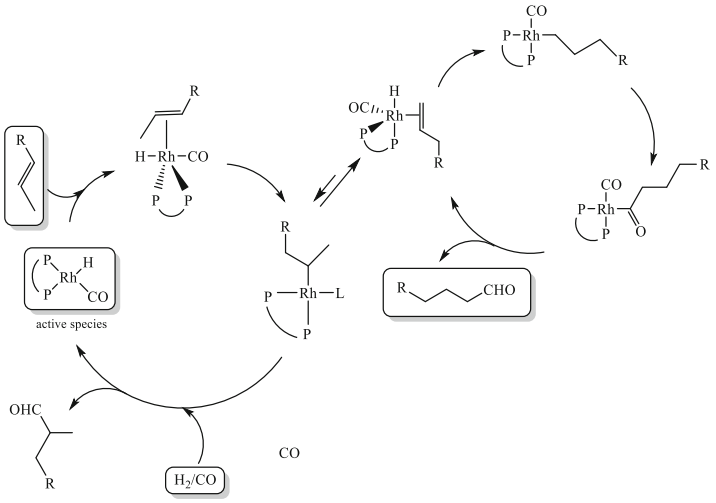
Scheme 2 Main steps for the hydroformylation of an alkene into the corresponding linear and branched aldehydes (the Rh(CO)(P$\widehat{\text{P}}$) framework has been reduced to [Rh] for the branched isomer cycle)

bond, coordination of one CO ligand followed by the migratory CO insertion in the alkyl chain, and then oxidative addition of dihydrogen give rise to the last intermediate of the catalytic cycle $[Rh(H)_2(COCH_2CH_2R)(CO)L_2]$. Release of the aldehyde by reductive elimination of one hydride and the acyl group regenerates the active $[Rh(H)(CO)L_2]$ species.

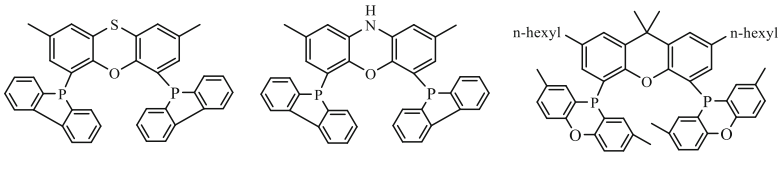
Scheme 2 shows the main steps of the hydroformylation reaction, in which a diphosphine ligand is coordinated to the rhodium metal center. In chapter Rhodium catalyzed hydroformylation (Carmen Claver), this reaction is detailed, particularly the parameters which govern the chemo-, the regio- and even the stereoselectivity of the reaction. The two catalytic cycles giving rise to the linear and the branched aldehydes are represented in two parallel ways. The discrimination between the two isomers arises in the step where the nucleophilic attack of the hydride ligand to the C_1 or C_2 carbon atoms of the coordinated C=C double bond occurs, from the δ^- hydride charge induced by the two phosphorus atoms bonded to the rhodium metal center.

2 Isomerization-Hydroformylation

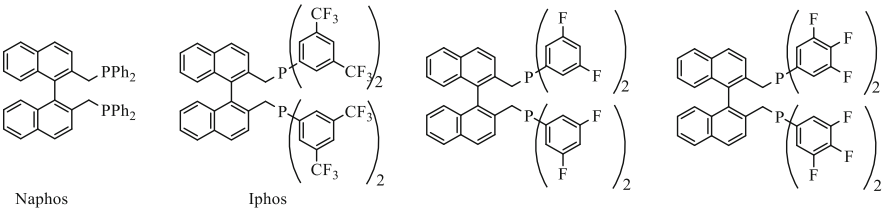
Instead of using terminal alkenes to produce aldehydes, preferably the linear ones in bulk chemistry, it is tempting from an economical point of view to start from internal alkenes or most of the time a mixture of terminal and internal alkenes such as found in Raffinate II (1-butene 64%, (*Z*)-2-butene 9%, (*E*)-2-butene 16%, traces of isobutene) after extraction of butadiene and isobutene from the C4 cut [12]. The tandem isomerization-hydroformylation reaction avoids to perform the separated isomerization reaction, since the thermodynamic mixture contains only around 5% of the terminal alkene. With an appropriate rhodium catalyst, which presents a high activity and selectivity for the hydroformylation of a terminal alkene, the tandem reaction is an elegant way to end up with terminal aldehydes [13, 14]. As previously stated [15], (1) the hydroformylation of the terminal C=C bond has to be fast compared with that of the internal one, (2) the isomerization rate must be fast compared to all hydroformylation reaction rates, and (3) the n/i ratio must be very high. Scheme 3 shows the two catalytic cycles in which the crucial connection line between the two catalytic cycles is the β-H elimination from the branched alkyl rhodium species to generate the terminal alkene coordinated to the metal center and the rapid formation of the terminal alkyl ligand through the hydride transfer onto the C_1 carbon atom. A diphosphine ligand has been represented on Scheme 3 since monophosphine ligands provide less attractive results in terms of selectivity for the terminal aldehyde starting from an internal alkene [16].



Scheme 3 Tandem isomerization of an internal alkene and hydroformylation into a terminal aldehyde



Scheme 4 Three crowded diphosphine ligands leading to a 96% selectivity in linear nonanal starting from (*E*)-oct-2-ene (from Refs. [18, 19])

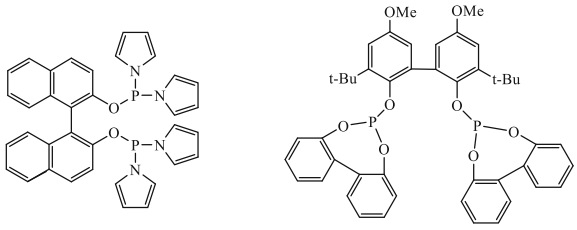


Scheme 5 Naphos, Iphos, and its difluoro- or trifluorophenyl analog ligands

The introduction of bulky chelating diphosphine ligands, with natural bite angles of around 112 and 129° [17], such as the two ligands drawn in Scheme 4, leads to performances comparable to those obtained early at an industrial scale [13]. At a low CO/H_2 pressure of 3.6 and even 2 bar and 120°C to enhance the rate of isomerization, it is possible to reach a highly selectivity in the isomerization-hydroformylation of (*E*)-oct-2-ene into nonanal, although a modest turnover frequency is observed [18].

Using the 2,7-di-n-hexyl-9,9-dimethyl-4,5-bis(10-dimethyl-phenoxaphosphino) xanthene ligand largely more soluble (118 mmol L^{-1}), kinetic studies reveal that for pent-2-ene, the reaction order is 0.6 in its concentration, consistent with a fast and reversible alkene coordination, and a −0.5 order in the CO pressure, indicative of a slow migratory CO insertion step justifying the use of low CO pressures (2–8 bar) [19]. Hydroformylation of pent-2-ene catalyzed by the $[Rh(acac)(CO)_2]$/Naphos system at 120°C and 10 bar provides a n/iso ratio of 89:11, although with modest reaction rates (TOF = 138 h^{-1}) [20]. The Iphos ligand (Scheme 5) containing electron-withdrawing substituents leads to significantly a more active and a selective catalyst, since but-2-ene and pent-2-ene give a 91:9 n/iso ratio with 66–68% yields, under the same conditions [20]. The performances are, respectively, 86:14 and 51% for oct-2-ene.

Using the 2,2′-bis(dipyrolylphosphinooxy)1,1′-binaphthyl bulky phosphinite chelating ligand (Scheme 6) combined to the $[Rh(acac)(CO)_2]$ complex, but-2-ene is transformed into n-pentanal at 120°C, 25 bar, with conversion of 90.5% in 6 h and regioselectivity n/iso = 95:5 obtained [21].



2,2'-bis(dipyrrolylphosphinooxy)-1,1'-binaphtyl Biphephos

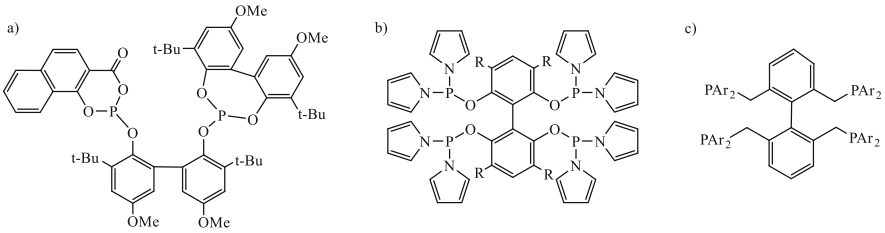
Scheme 6 2,7-di-n-hexyl-9,9-dimethyl-4,5-bis(10-dimethyl-phenoxaphosphino)xanthene from Ref. [21] and Biphephos from Ref. [13]

Sulfonated Naphos, which is a mixture a sodium salts of different regioisomers with a 6-8 sulfonation degree of the phenyl groups between 6 and 8, so-called Binas [22, 23], allows to perform the reaction in a biphasic water system [24]. It is necessary to adjust the pH of the water phase to 7–8 with phosphate buffer in order to obtain a 72–73% yield C_6 aldehydes starting from pent-2-ene and a n/iso regioselectivity of 99:1. The same performances are reached by addition of amines in water such as triethanolamine or triisooctylamine, showing that the increase in the reactivity is due to the adjustment of the pH and not to the transfer of the catalyst in the organic phase [24].

Performing the isomerization-hydroformylation of oct-4-ene to obtain n-nonanal in propylene carbonate instead of toluene, in the presence of $[Rh(acac)(CO)_2]$ and five equivalents of the Biphephos diphosphite ligand (2,2′-bis[(2,2′bisphenoxy) phosphino]-oxy-3,3′,5,5′-tetra-tert-butyl-1,1′-biphenyl) (Scheme 6) at 125°C and 20 bar, provides 95% selectivity in n-nonanal [25]. Five runs can be performed, leading to the same catalytic performances. This reaction can be operated in a temperature-dependent multicomponent system (TMS) to suppress the catalyst leaching. For instance, with a cyclic carbonate/*N*-octyl-pyrrolidone/n-dodecane system, which gives only one phase at 125°C but two phases at room temperature, the conversion of (*E*)-oct-4-ene is 99%, with a 80% regioselectivity in *n*-nonanal, the leaching in rhodium is <0.1% and in phosphorus of 0.6% [26]. This tandem reaction applied to methyl oleate, with an original diphosphite ligand leading to the eq,eq-$[Rh(H)(CO)_2L_2]$ precursor, allows to isomerize the C=C double bond in 9-position to give 75% of linear aldehyde selectivity [27].

The difluorophenyl analog of Iphos (Scheme 5) gives 94:6 n/iso ratio and 59% yield for pent-2-ene, and the trifluorophenyl analog (Scheme 5) gives 94:6–95:5 and 61–74% for both but-2-ene and pent-2-ene and even 70:30 and 41% after 31 h for oct-2-ene [20]. The unsymmetrical ligand of Scheme 7a is able to give rise to 69% of n-nonanal starting from a mixture containing 94% internal alkenes with high reactivity since the TOF is 4,448 h^{-1} at 130°C and 20 bar [28].

The tetraphos ligand (R=H of Scheme 7b) added to $[Rh(acac)(CO)_2]$ in a ligand/metal = 3:1 ratio appears as particularly efficient, presumably because of its enhanced chelating ability with regard to diphosphine ligands [29]. Indeed, at 100°C and 10 bar of a CO/H_2 gas mixture for 1 h, n/iso = 98:2 ratio is obtained

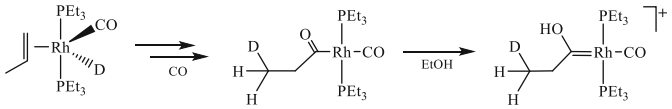


Scheme 7 Unsymmetrical diphosphite ligand (from Ref. [28]) and tetraphos ligands (from Refs. [29–31])

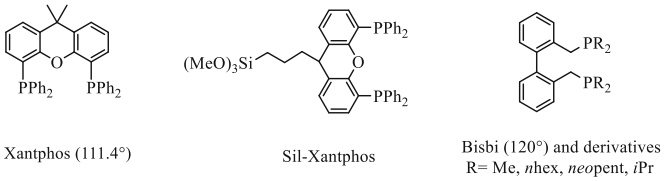
with a 1,500 turnover number (TON) for oct-2-ene and for hex-2-ene 98.8:1.2 and TON=1,700. Introduction of Cl, Me, Et, Ph, tolyl, and *p*FPh substituents in the 3,3′,5,5′ positions (R≠H) still increases the efficiency of this isomerization for these two substrates [30]. Similarly the tetraphosphine ligand based on a biphenyl backbone (Scheme 7c) gives regioselectivities close to 99:1 at 120°C, 5 bar, for a L/Rh = 4 ratio, particularly when the Ar group is the electron-withdrawing 3,5-$F_2C_6H_3$ substituent [31]. Analog bidentate phosphite ligands containing two bisphosphoramidite entities bound to a spiroketal backbone provide the isomerization-hydroformylation of but-2-ene and oct-2-ene with regioselectivities close to 95–97% and TONs as high as 27,000. The X-ray crystal structure of the $[Rh(acac)L_2]$ complex, as well as infrared and ^1H, ^{31}P NMR analyses of the $[Rh(H)(CO)_2L_2]$ in situ prepared show that the P-Rh-P bite angle is 94.7°, and the phosphorus atoms occupy two equatorial positions of the trigonal bipyramid [32], as already shown for the 1,1′-biphenyl-2,2′-diyl-bis(dipyrolylphosphoramidite) ligand [33]. Similar high-pressure NMR spectroscopic data on rhodium-crowded bidentate diphosphites are consistent with an energetically preferred bis-equatorial mode of coordination in the trigonal-bipyramidal $[Rh(H)(CO)_2L_2]$ resting state and being efficient in this tandem reaction [34, 35].

3 Hydroformylation-Hydrogenation

Alcohols, particularly linear alcohols, have broad applications as solvents and raw materials for plasticizers and detergents. Thus, the tandem hydroformylation-hydrogenation reaction allows to directly synthesize the alcohol from an alkene, provided a specific catalytic system leads to a high selectivity at a reasonable reaction rate. In the early stages of the "oxo" reaction, the formation of alcohols has been observed. The Shell process involving the $[Co(H)(CO)_3(PBu_3)]$ catalyst allows to produce directly butanol from propene at high temperature and pressure [36]. Working under the mild conditions of Rh-oxo synthesis, patents claim that (β-diketone)Rh [37] or $[(\eta^5\text{-}C_5H_5)Rh(CO)(PBu_3)]$ precursors [38] catalyze the formation of alcohols. Starting from the $[Rh(H)(PEt_3)_3]$ precursor hex-1-ene is fully transformed into heptanol at 120°C and 40 bar $CO/H_2 = 1:1$ in ethanol, or



Scheme 8 Partial catalytic steps leading to a cationic hydroxycarbene-rhodium species in ethanol (adapted from Ref. [40]). The counter-anion is presumably EtO^-



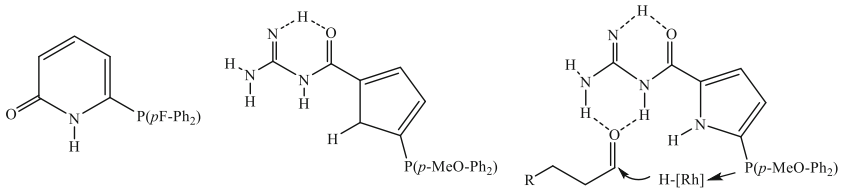
Scheme 9 Xantphos, its trimethoxysilane-*n*-propyl version, and Bisbi's derivatives (from Refs. [41, 42])

an alcoholic solvent, with an initial TOF of 2,300 h^{-1} and the n/iso ratio ca 2.8:1 [39, 40]. Using D_2-CO labeling studies, ^1H and ^{31}P NMR analyses allow to identify the $[Rh(H)(CO)(PEt_3)_2]$ active species. They are consistent with the protonation of the acyl intermediate by ethanol to generate an hydroxycarbene-rhodium species which reacts with H_2 to provide after reductive elimination the final alcohol (Scheme 8) [40].

The introduction in the coordination sphere of rhodium of Xantphos-type ligands immobilized on silica (Scheme 9) transforms oct-1-ene into n-nonanol with 90% selectivity in the linear alcohol [41]. The reaction is carried out in toluene, since it simultaneously involves the two species $[Rh(polySil\text{-}Xantphos)(CO)]^+$ and $[Rh(H)(CO)_2(polySil\text{-}Xantphos)]$. In *n*-propanol solvent, the hydrogenation activity is suppressed and 93–95% of linear aldehyde are obtained, presumably by deactivating the acidic silanols on the silica surface. By comparison the complex $[Rh(H)(CO)_2(Xantphos)]$ is active for the hydroformylation reaction with around 25% of hydrogenation of oct-1-ene into octane, whereas the cationic $[Rh(CO)(Xantphos)]^+[CF_3COO)]^-$ complex is active for the hydrogenation of nonanal.

The large bite angle Me-Bisbi ligand (Scheme 9) is interesting since, added to $[Rh(acac)(CO)_2]$, the resulting catalytic system in ethanol gives 97% of the C_{11} alcohols from dec-1-ene with a n/iso = 80:20 ratio at high temperature of 170°C [42]. The simultaneous use of PEt_3 and the wide bite angle diphosphines such as Xantphos or Diop with $[Rh(acac)(CO)_2]$ leads to a mixed complex very efficient to do this tandem reaction and to obtain heptanol from hex-1-ene in 90% yield with n/iso = 99:1 ratio. Similar performances are observed with oct-1-ene and dec-1-ene, as well as allyl alcohol providing butanediol [43].

This strategy of the cooperative ligand system is adopted to define the best catalytic tool able to perform the two distinct hydroformylation and hydrogenation reactions with high selectivity. Indeed, the simultaneous addition of 6-di(*p*-fluorophenyl)phosphanylpyridone and acylguanidyl-pyrrolyldi(*p*-methoxy)

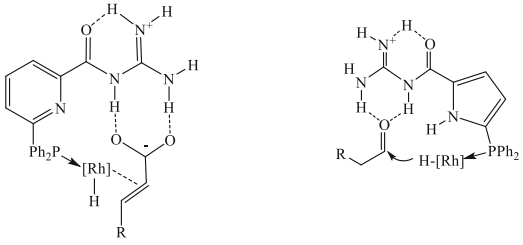


6-di(*p*-fluorophenyl) phosphanylpyridone

acylguanidyl-pyrrolyldi(*p*-methoxy)phenylphosphine

key step for the aldehyde hydrogenation

Scheme 10 The two phosphanylpyridone and acylguanidyldiphenylphosphine ligands leading to a cooperative action in the hydroformylation-hydrogenation of an alkene (from Ref. [44])



(2-acylguanidyl-pyridyl) diphenylphosphine

(2-acylguanidyl-pyrrolyl) diphenylphosphine

Scheme 11 The two key steps in the decarboxylative hydroformylation-hydrogenation reaction of α,β-unsaturated carboxylic acids using two supramolecular bifunctional ligands (from Ref. [45])

phenylphosphine (1:1) (Scheme 10) to [Rh(acac)$(CO)_2$] leads to an efficient catalytic system to gain alcohols with 95% conversion and n/iso = 96:4 regioselectivity [44]. A wide range of substrates were evaluated and selectively transformed under the same operating conditions (20 bar, 80°C, toluene, 24 h). The acylguanidyl ligand is responsible for the hydrogenation step, and it is suggested that two NH bonds interact with the aldehyde to favor the Rh-H transfer to reduce the carbonyl group into the alcohol (Scheme 10).

Taking advantage of the recognition of functional groups by the acyl guanidinium functionality, association of the two ligands of Scheme 11 is responsible for the novel tandem decarboxylative hydroformylation-hydrogenation of α,β-unsaturated carboxylic acids [45]. In the key step, the C=C bond coordinates to the rhodium metal center, whereas the guanidine group interacts with the two oxygen atoms of the acidic function, to remove CO_2; in the second key step, the aldehydic function interacts with the guanidine group to assist the hydride transfer.

The tandem hydroformylation-hydrogenation reaction has been applied to the isoprene substrate. Addition of a large excess (15:1) of the bis(diphenylphosphino) ethane ligand (dppe) to [Rh(acac)$(CO)_2$] induces the classical 1,4-hydroformylation of isoprene [46], but the next step is the hydrogenation of the C=C double bond to synthesize 3-methylpentanal [47]. The reaction, performed in cumene at 100°C, 50 bar, and during 24 h, leads to 85% yield in the saturated aldehyde, and no alcohol is detected [47]. The dppe role is also to induce the oxidative addition of dihydrogen

to the 2,3-unsaturated acyl-rhodium intermediate leading to the conjugated unsaturated aldehyde, which is further rapidly hydrogenated.

4 Hydroformylation-Acetalization

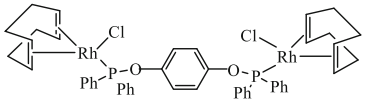
As rhodium complexes, such as $[RhCl_2(MeCN)\{MeC(CH_2Ph_2)_3\}][CF_3SO_3]$, are able to catalyze the acetalization of aldehydes or ketones under mild conditions [48], the direct synthesis of acetals from an alkene by the tandem hydroformylation-acetalization reaction is shown to be effective in the presence of $[Rh_2(\mu\text{-}OMe)_2(COD)_2]$/10 PPh_3 at 60–90°C under 50 bar of a $CO/H_2 = 1{:}1$ gas mixture [49]. A weak acid as pyridinium *p*-toluenesulfonate or camphorsulfonate is required as well as 2,2-dimethoxypropane or triethylorthoformate to introduce the two alkoxy functions. Thus 2,5-dihydrofuran, styrene, 5-methyl-hex-5-ene-2-one, or vinylacetate are almost fully converted into the corresponding acetals (95–97%) [49].

The synthesis of the dirhodium complex bridged by a diphosphinite ligand (Scheme 12) leads to a good catalyst for the tandem reaction of hex-1-ene in methanol, operating at 30 bar, 80°C, for 8 h. It gives 99% selectivity in aldehyde for 100% conversion, although the n/iso ratio is only 46:54 [50]. This reaction has been extended with the same efficiency to styrene and its substituted analogs with donating or withdrawing substituents and cyclopentene or cyclohexene.

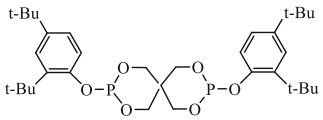
Using the crowded diphosphite ligand drawn on Scheme 12 with $[Rh(acac)(CO)_2]$ results in 85% yield in acetals at 20 bar, 110°C, for 6 h, starting from various allylbenzene substrates [51].

Introducing four equivalents of $P(OPh)_3$ to the two dirhodium $[Rh_2\{\mu\text{-}SCR_2CH(NH_3)^+(COOH)\}_2(CO)_4][CF_3SO_3]_2$ catalytic precursors (with R=H cysteine bridging ligand and R=Me, penicillamine) allows to obtain high yields of the acetals starting from (1*R*,4*R*)-isolimonene and (−)-β-pinene with triethylorthoformate (Scheme 13) [52]. Glucal derivatives are similarly transformed into acetals using the $[Rh_2(\mu\text{-}OMe)_2(COD)_2]$/10 P(O-*o*-Bu^{t}Ph)$_3$ catalytic system (Scheme 13) [53].

The $[Rh_2\{\mu\text{-}SCH_2CH_2(NHMe_2)\}_2(CO)_2(PPh_3)_2][CF_3SO_3]_2$ complex anchored to a sulfonic exchange resin catalyzes this tandem reaction in methanol with a small leaching of rhodium. Styrene is fully converted into dimethyl acetal, with ca 85% selectivity into the branched product [54]. Direct use of the $RhCl_3{,}3H_2O$/2 P$(OPh)_3$ catalytic system leads to high yields in the acetals corresponding to styrene

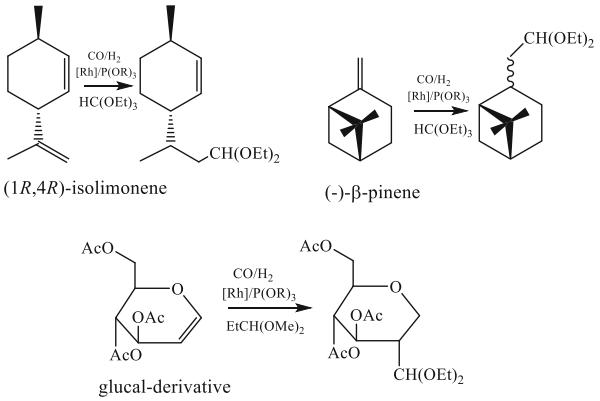


1,4-bis(diphenylphosphinoxy)benzene



[bis(2,4-di-*tert*-butyl)pentaerythritol]diphosphite

Scheme 12 Dirhodium precursor with a bridging diphosphinite ligand (from Ref. [50]) and [bis(2,4-di-*tert*-butyl)pentaerythritol]diphosphite (from Ref. [51])



Scheme 13 Tandem hydroformylation-acetalization of isolimonene and β-pinene (from Ref. [52]) and 3,4,6-tri-*O*-acetyl-D-glucal and related glucal derivatives (from Ref. [53])

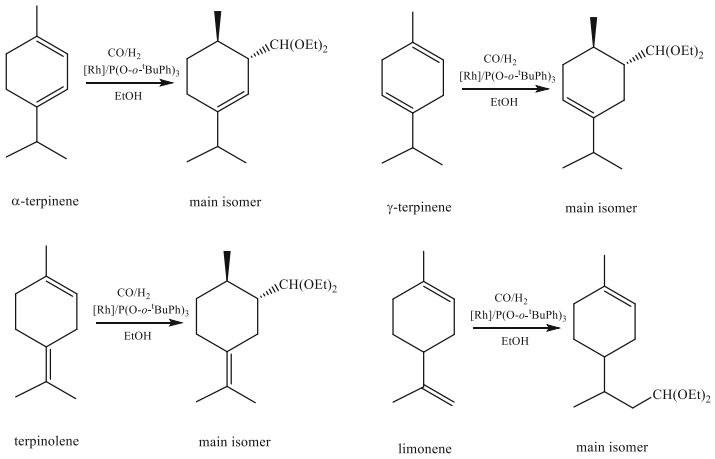
and oct-1-ene, in methanol [55] but not in triethylorthoformate, which gives exclusively aldehydes [56]. The $Rh^{(III)}$ precursor ($RhCl_3$,$3H_2O$) can be anchored on mesoporous silica MCM-41 support, eventually in the presence of the $H_3PW_{12}O_{40}$ heteropoly acid, that increases the yield of acetals to 92%, even if the leaching of rhodium remains too high [57]. The *cis*-$[Rh(CO)_2(amine)_2][PF_6]$ complexes, with amine being pyridine, picoline, or lutidine, transform hex-1-ene, still in methanol, under 0.9 bar of only CO at 100°C, in similar quantities of the methyl ester (by methoxycarbonylation) and the 1,1-dimethoxyheptane acetal, dihydrogen being produced by the water-gas shift reaction [58]; the reaction can be also performed with the cationic complex immobilized on poly (4-vinylpyridine) [59].

Another immobilization method involves triphenylphosphine functionalized on one phenyl in 4-position with a glycine group. The zwitterionic NH_3^+-CH_2-COO^- group, allows to prepare a Brönsted acid-rhodium bifunctional catalyst to keep it in an ionic liquid [60]. No significant loss of rhodium is observed during at least 12 recycling experiments for the hydroformylation-acetalization of oct-1-ene.

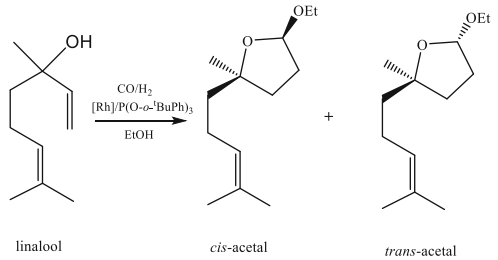
The $[Rh_2(\mu\text{-OMe})_2(COD)_2]$/$P(O\text{-}o\text{-}Bu^tPh)_3$ catalytic system (P/Rh = 20–50) is largely more active than with the PPh_3 phosphorus ligand and allows to convert in ethanol at 80°C and 80 bar (CO/H_2 = 1:1) α-terpinene, γ-terpinene, terpinolene, and limonene into the corresponding diethylacetals (Scheme 14) [61].

This procedure has been extended to the synthesis of other fragrance compounds from acyclic monoterpenes such as linalool and β-citronellene [62]. Excellent selectivity in the formation of the cyclic acetals from linalool is obtained. Two *cis*- and *trans*-stereoisomers are formed, the *cis*- being the major isomer (Scheme 15). For β-citronellene the reaction is less efficient since a mixture of aldehydes and acetals is obtained whatever the experimental conditions explored. This reaction is performed in ethanol with the bulky phosphite ligand in the absence of additional acid cocatalyst under mild conditions.

As hydroformylation of unsaturated alcohols results in cyclic hemiacetals [10, 62, 63], this tandem reaction has been explored on alkenediols, especially



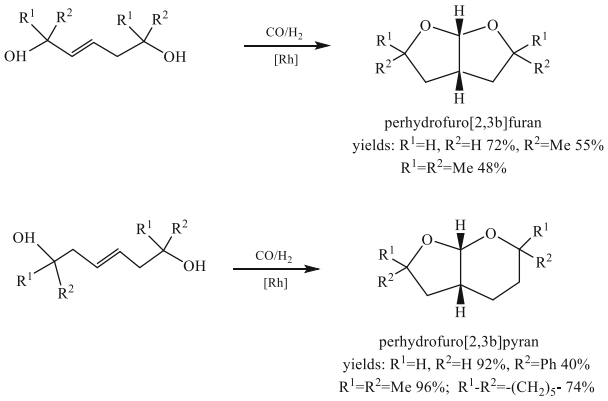
Scheme 14 Main acetal isomers obtained by hydroformylation of α-terpinene, γ-terpinene, terpinolene, and limonene with the $[Rh_2(\mu\text{-}OMe)_2(COD)_2]/P(O\text{-}o\text{-}Bu^tPh)_3$ catalyst in ethanol (from Ref. [61])



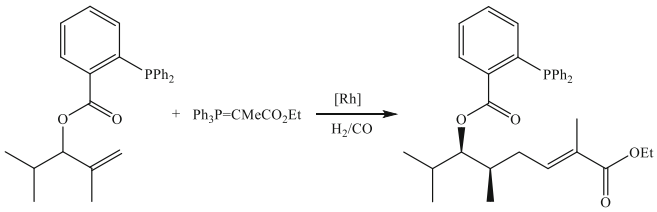
Scheme 15 The two cyclic acetals produced in ethanol by hydroformylation-acetalization of linalool (from Ref. [62])

since active pharmacodynamic compounds such as aflatoxins possess a furo[2,3*b*] skeleton [64]. Thus, operating with $[Rh_2(\mu\text{-}OMe)_2(COD)_2]/PPh_3$ (P/Rh = 6), at 120°C for 20 h under 60 bar of a $CO/H_2 = 3{:}1$ mixture, pent-2-ene-1,5-diol as well as hex-2-ene-1,6-diol, and some of their substituted analogs provides the corresponding perhydrofuro[2,3b]furans or perhydrofuro[2,3*b*]pyrans through a double acetalization-cyclization process (Scheme 16).

Concerning the mechanism of the acetal formation in methanol, especially in the absence of acid added, several studies have shown that the $[Rh(COD)_2][BF_4]$ or $[Rh_2(\mu\text{-}Cl)_2(COD)_2]$ precursors, in the presence of a diphosphine [65] or PPh_3 ligand [66], as well as molecular hydrogen, are required to obtain a good acetal selectivity. There is a cooperative effect between the rhodium complex and the in situ formed acid HBF_4 or HCl. The hydroformylation is fast, for instance, the TOF is 1,000 h^{-1} with $[Rh(COD)_2][BF_4]$/Xantphos at 30 bar and 110°C, and the acetalization is the limiting step with a TOF = 120 h^{-1} [65].



Scheme 16 Tandem hydroformylation-acetalization of α,ω-alkenediols into the corresponding bicyclic acetals (from Ref. [64])

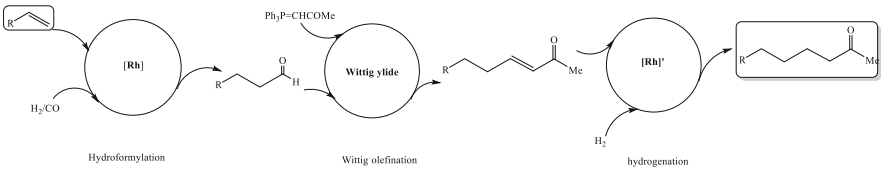


Scheme 17 Stereoselective formation of a trisubstituted C=C bond by tandem hydroformylation-Wittig reaction (from Ref. [68])

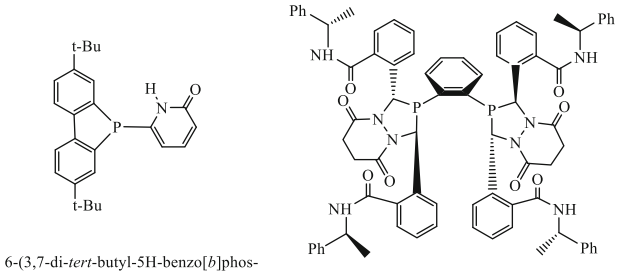
5 Hydroformylation-Wittig Olefination

The classical Wittig olefination results from the reaction of an aldehyde or a ketone with a phosphonium ylide to synthesize an alkene, coproducing a phosphine oxide [67]. This tandem reaction has been developed since the first demonstration reported that a methallyl protected alcohol could react with $Ph_3P{=}CMeCOOEt$ or $Ph_3P{=}CMeCOMe$ and be transformed into an α,β-unsaturated carbonyl derivative with 75–78% yields. Moreover the attachment of the *ortho*-diphenylphosphanylbenzene (*o*-DPPB) group to the alcohol function transforms the corresponding trisubstituted alkene with a high *syn*/*anti* = 96:4 diastereoselectivity (Scheme 17) [68]. Due to the second stereogenic center formed, the diastereoselectivity is controlled by the *o*-DPPB directing group in the course of the hydroformylation reaction. The *E*-selectivity of the double bond is due to the high *E*-preference of phosphorus ylides.

The success of this tandem reaction requires working with stabilized phosphorus ylides.



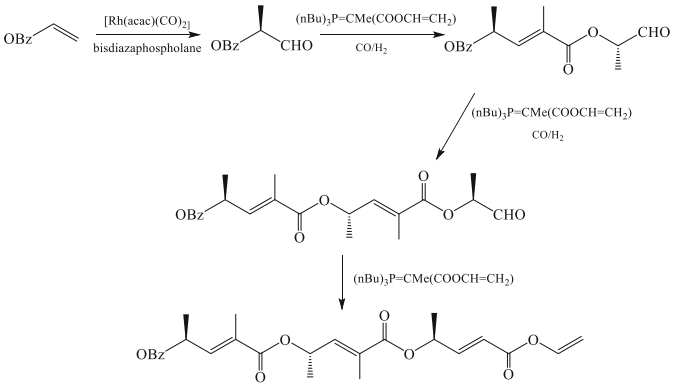
Scheme 18 Tandem reaction involving hydroformylation-Wittig olefination and hydrogenation of the unsaturated carbonyl compound



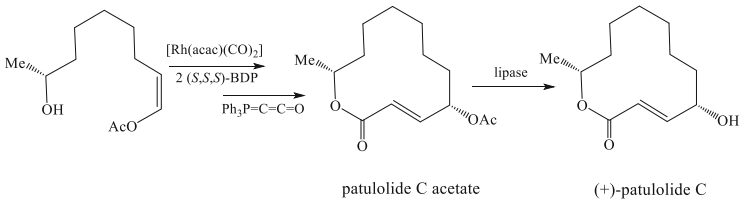
Scheme 19 Two efficient dibenzophosphole and bisdiazaphospholane ligands used in the hydroformylation-Wittig olefination tandem reaction (from Refs. [71, 72])

Saturated ketones (Scheme 18), still containing the *o*-DPPB group, are produced with 70% yield and *syn*/*anti* = 92:8 diastereoselectivity when the non-disubstituted Ph_3P=CHCOMe ylide is introduced in the one-pot reactor [68]. The third step is the hydrogenation of the C=C double bond, catalyzed by the rhodium complex, as shown by independent tests involving $[Rh(H)(CO)(PPh_3)_3]$ under H_2 [69]. In this case the tandem hydroformylation-Wittig olefination-hydrogenation process is realized.

The same catalytic system involving the Xantphos or Biphephos ligands allows to obtain full conversions of N-protected allylamine into ca 85% α,β-unsaturated carbonyl compounds using Ph_3P=CHCOX (X = Me, OMe, N(OMe)Me) and to reduce the amounts of the saturated ester to ca 15% [70]. Moreover, the reaction with Biphephos can be carried out at 50°C and under atmospheric pressure of a $CO/H_2 = 1:1$ gas mixture, allowing to obtain selectivity up to 98% in unsaturated carbonyl compounds. Deprotection of the nitrogen atom by elimination of the formyl or Boc group, followed by an intramolecular aza-Michael addition, gives *trans*-2,5-disubstituted pyrrolidines with a 94–97% enantiomeric excess. The scope of the reaction is done with a variety of allylamine derivatives. Various homoallylic alcohols can be transformed in 7-hydroxyenoates at 3 bar of $CO/H_2 = 1:1$, 80°C, for 16 h with $[Rh(acac)(CO)_2]$/dibenzophosphol derivative (shown in Scheme 19), which gives the most satisfactory chemo- and regioselectivity. The enoates can be further cyclized through an oxa-Michael addition reaction to produce the



Scheme 20 Hydroformylation-Wittig olefination sequences with the $[Rh(acac)(CO)_2]$/(*S*,*S*,*S*)-bisdiazaphospholane catalytic system and the allyl-substituted $(nBu)_3P{=}CMe(COOCH{=}CH_2)$ ylide (from Ref. [72])



Scheme 21 Tandem hydroformylation-Wittig olefination of 9-acetoxy-*Z*-(2*R*)-8-nonene-2-ol into patulolide acetate, transformed into (+)-patulolide C with *Pseudomonas fluorescens* lipase (from Ref. [73])

corresponding *cis*-pyrans in 87–91% yields and excellent diastereoselectivities [71].

An efficient enantioselective one-pot hydroformylation-Wittig olefination has been designed to produce γ-chiral α,β-unsaturated carbonyl compounds. The chiral bis(diazaphospholane) ligand (Scheme 19) coordinated to rhodium transforms vinylacetate into the branched aldehyde in the first step with an excellent enantioselectivity (up to 99%) followed by the Wittig olefination with stabilized ylides [72].

Multiple iterative hydroformylation-Wittig olefination sequences can be performed with successive depressurization and repressurization steps to provide an aldehyde from the diene intermediate obtained. Concerning the tandem reaction, the aldehyde resulting from the sequential reactions with the vinylbenzoate substrate and the $(nBu)_3P{=}CMe(COOCH{=}CH_2)$ ylide, leads to the 4-hydroxyvalerate trimer with three unique stereocenters in a 17% isolated yield (Scheme 20) [72].

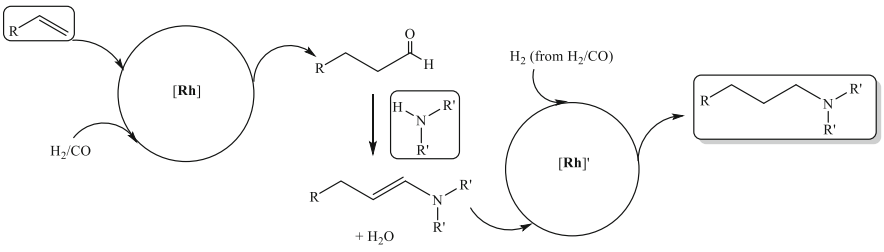
The patulolide C acetate macrolactone is synthesized by the same procedure (Scheme 21) [73]. The 9-acetoxy-*Z*-(2*R*)-8-nonene-2-ol substrate, obtained by acetoxylation of (2*R*)-8-nonyn-2-ol, is transformed at 14 bar of syn gas, at 50°C,

for 24 h and then in the presence of the $Ph_3P{=}C{=}C{=}O$ ylide into the corresponding 12-membered lactone, with complete *E*-selectivity. Deacetylation with a lipase proceeds in quantitative yield to give (+)-patulolide C with a 97% diastereoselectivity.

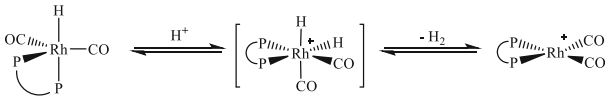
6 Hydroaminomethylation

As rhodium complexes are able to catalyze both the Hydrogenation [74] and hydrogenation reactions [75] (cf. *also part* Hydroformylation-Hydrogenation *of this chapter*), the hydroaminomethylation reaction (HAM), shown in Scheme 22, has been significantly investigated and some reviews have recently appeared [76, 77]. HAM represents an attractive atom economy reaction providing amines from alkenes in a one-pot way. Moreover, the reactants are generally abundant and cheap building blocks. This tandem reaction is composed of three successive steps. Aldehydes produced by the first catalytic hydroformylation reaction react with ammonia, or primary or secondary amines present in the medium, to afford the corresponding imines or enamines. The linear aldehyde is largely more reactive than the branched one in this condensation reaction. Most of the time, isomerization between imine and enamine occurs, and hydrogenation of these two intermediates in the second catalytic cycle results in the formation of the expected amines.

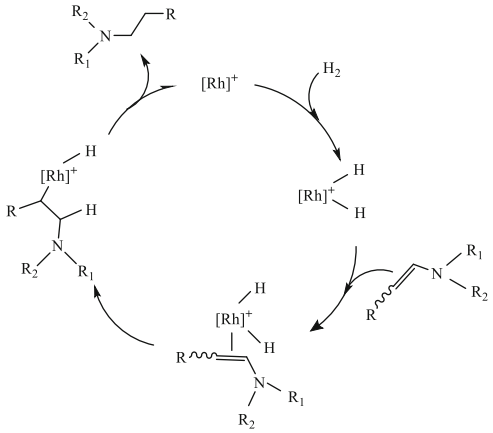
It is necessary to carefully control the design of the catalytic system in order to have not only high chemoselectivity but also regioselectivity depending of the branched or linear expected final amine. Indeed the hydrogenation reaction is the rate determining step in HAM. Recently, it has been demonstrated that an equilibrium between the neutral $[Rh(H)(CO)_2L_2]$ and the cationic $[Rh(CO)(X)L_2]^+$ species exists to perform the two catalytic cycles [78]. Presumably, the neutral rhodium-hydride species catalyzes the hydroformylation reaction, whereas the cationic species performs the hydrogenation reaction. Instead of using simultaneously a cationic and a neutral rhodium precursor in order to increase both catalytic activity and amine selectivity [79], it is preferable to have an appropriate rhodium system



Scheme 22 The two catalytic cycles involved in the tandem hydroaminomethylation reaction (only the linear products are represented)



Scheme 23 Equilibrium between the neutral rhodium-hydride complex and the cationic square-planar complex (from Ref. [78])



Scheme 24 Catalytic cycle for the hydrogenation of an enamine (the active species is just represented as $[Rh]^+$ for more clarity)

able to generate in situ the two catalytic active species which remain in equilibrium (Scheme 23).

Scheme 24 is devoted to the R-CH=CH-NR_1R_2 enamine hydrogenation, showing the main catalytic steps. Classically, the cationic active species, represented as $[Rh]^+$, reacts with dihydrogen by an oxidative addition reaction to give a dihydride which coordinates the enamine. The hydride transfer, and then the reductive elimination leads to the final amine, restoring the $[Rh]^+$ active species.

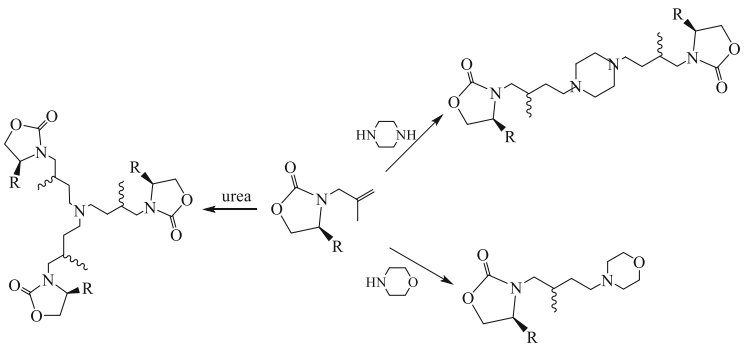
To reach good yields in amines, this tandem reaction is generally performed in the 90–130°C temperature and 30–60 bar of CO/H_2 range. These operating conditions are somewhat more severe than those for the hydroformylation reaction consistent with a rate determining step for the hydrogenation reaction of imines/enamines. The CO/H_2 composition generally varies from 1:1 to 1:5 depending on the experimental procedures.

In the following part, we analyze the various performances of the catalysts according to the nature of the alkene and in some cases that of the amine, giving the most attractive performances.

6.1 Hydroaminomethylation of Terminal and Internal Alkenes

With an efficient catalytic system, the hydroformylation reaction quickly proceeds, especially for the terminal alkenes, so no isomerization of the C=C double bond occurs. Thus the two linear and iso- (on the C2 carbon atom) aldehydes are formed, and after hydrogenation of the enamines/imines, the n- and iso-amines are produced. However, for most amines the two isomers possess similar physical properties, making their separation difficult for obtaining pure products. Many efforts have been made to adjust the coordination sphere of the catalyst in order to reach regioselectivities as high as 98:2 to obtain directly the linear isomer. This goal has been achieved by using diphosphine ligands. Indeed, whereas triphenylphosphine generates the $[Rh(H)(CO)(PPh_3)_3]$ resting state and gives rise to a 86:14 n/iso ratio, the use of the Xantphos ligand (Scheme 9) and $[Rh(COD)_2]BF_4$ precursor combines not only the quantitative conversion of different terminal alkenes but also the fast hydrogenation of the enamine/imine (ca 97%) and a high 98:2 n/iso ratio [80]. The conditions are $CO/H_2 = 7{:}33$ bar, 125°C, and 5 h in a 1:1 toluene/methanol mixture. Using these two solvents allows to suppress the formation of *N*-formylpiperidine which is produced in pure methanol up to 15%. Introducing the $[Rh_2(\text{-}\mu\text{-}Cl)_2(COD)_2]$ or $[Rh(acac)(CO)_2]$ precursors with four equivalents of Xantphos ligand gives a lower selectivity in amines (94 and 90%, respectively). In addition the two dppe 1,2-bis(diphenylphosphino)ethane and Iphos diphosphines (Scheme 5) give rise to less interesting performances even if Iphos leads to n/iso ratio of 99:1. This latter ligand combined with $[Rh(acac)(CO)_2]$ proves to be a powerful catalyst to the one-pot synthesis of hydrazones from terminal alkenes and hydrazines since at 65°C under 10 bar CO/H_2 (1:1), the alkenes are converted in 16 h into the expected hydrazones with selectivities ranging from 85 to 99% and n/iso ratios of 99:1 except for functionalized alkenes (88:12–98:2) [81]. Moreover, it is possible, after catalysis, to add four equivalents of $ZnCl_2$ to the crude reaction mixture for obtaining by heating for several hours the corresponding indoles. Starting from pent-1-ene or allyl phenyl ether and *N*-phenylhydrazine, excellent yields of 80–85% and n/iso = 99:1 regioselectivity are obtained [81].

The $[Rh(COD)_2]BF_4$/Xantphos catalytic system was explored for various alkenes under the following conditions: 60 bar ($CO/H_2 = 10{:}50$) and 95°C for 12 h. The HAM reaction starting from pent-1-ene and piperidine, morpholine, thiomorpholine, *N*-benzylpiperazine, dimethylamine, and aniline produces the corresponding amines with the hexyl fragment. The same reaction from pent-1-ene and the primary hexylamine generates dihexylamine and, with this latter amine, the trihexylamine. For all these substrates, the conversions and chemoselectivity as well as the regioselectivity (98:2–99:1) are very attractive. The piperidine reactant has also been used with hex-1-ene, oct-1-ene, and various substituted alkenes. In all these experiments, the performances are high for the three selectivity parameters [80].



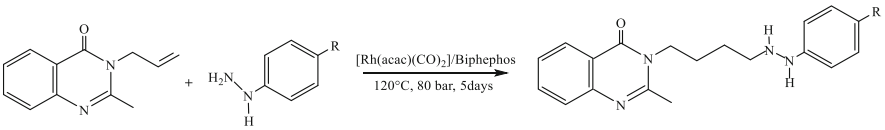
Scheme 25 Hydroaminomethylation of *N*-methylallyloxazolidinone (adapted from ref [82])

Due to the presence of their N–O functional groups, chiral amino alcohols are useful vectors to assist catalysis by chiral recognition and combinatorial approach. They can be obtained by hydrolysis of oxazolidinone moieties in which the amino alcohol is protected. Following this strategy, *N*-olefinic oxazolidinones (R = Ph, CH_2Ph, *i*-Pr) have been used to perform HAM with various amines.

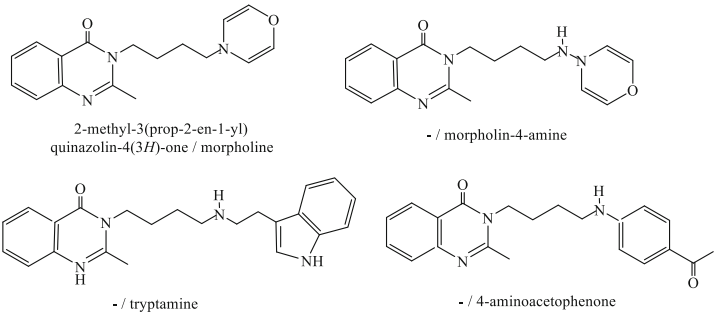
As shown in Scheme 25, the reaction with morpholine, piperazine, and urea gives the corresponding amines with high yields (79–95%) and total regioselectivity. However no chiral induction is observed during the hydroformylation step or the reduction of the imines/enamines [82]. The catalytic $[Rh_2(\mu\text{-}Cl)_2(COD)_2]$ precursor operates at 120°C and 60 bar ($CO/H_2 = 1{:}1$) in dioxane for 48–72 h. This reaction can be extended to tris(aminoethyl)amine, N $(CH_2CH_2NH_2)_3$, providing after 120 h the formation of the corresponding dendritic polyamines containing 6 oxazolidinone (no s) moieties. The same reaction involving N-allyloxazolidinone requires the use of the $[Rh(acac)(CO)_2]$/Biphephos (cf. Scheme 6) catalytic system to obtain the linear aldehyde in n/iso = 87:13 regioselectivity in dioxane at 50°C under 20 bar ($CO/H_2 = 1{:}1$) for 48 h. In a second step, the reductive amination of the aldehydes is performed after adding piperazine or 1-(3,5-bis(piperazin-1-yl)methylbenzyl)piperazine and repressurizing under 60 bar ($CO/H_2 = 1{:}5$) to obtain the two dendritic polyamines. Their hydrolysis leads to the two corresponding aminoalcohols. These chiral aminoalcohols are used as ligands for $[RuCl_2(p\text{-cymene})]_2$ catalytic precursor in the asymmetric hydrogen transfer reaction [82].

The $[Rh(acac)(CO)_2]$/Biphephos system also catalyzes the reaction of 2-methyl-3(prop-2-en-1-yl)quinazolin-4(3*H*)-one with arylhydrazines at 120°C and 80 bar ($CO/H_2 = 70{:}10$) for 5 days, resulting in the formation of the linear amines with yields as high as 96% and regioselectivity of around 90:10 (Scheme 26) [83].

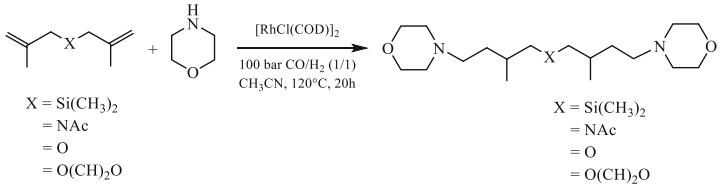
Similarly, starting from 2-methyl-3(prop-2-en-1-yl)quinazolin-4(3*H*)-one and morpholine, morpholine-4-amine, tryptamine, and 4-aminoacetophenone, $[Rh(acac)(CO)_2]/P(OPh)_3$ produces the four linear amines represented on Scheme 27. The yields after purification by column chromatography are 89, 93, 78, and 67%, respectively [83]. This high yield method for synthesizing 3-substituted quinazolin-



Scheme 26 HAM reaction of 2-methyl-3(prop-2-en-1-yl)quinazolin-4(3*H*)-one with arylhydrazine (adapted from ref [83])



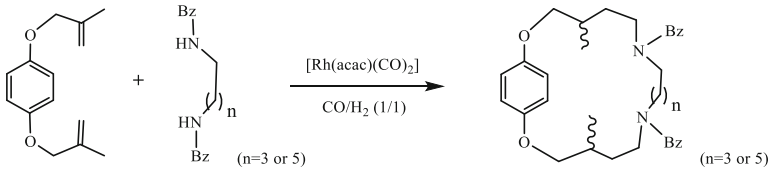
Scheme 27 Hydroaminomethylation reaction involving 2-methyl-3(prop-2-en-1-yl) quinazolin-4 (3*H*)-one with four amines (adapted from ref [83])



Scheme 28 Hydroaminomethylation of bis(methallyl)silanes, bis(methallyl)amines, and bis (methallyl)ether (adapted from ref [86])

4(3*H*)-ones is of great interest since these compounds have a biological activity, particularly for the central nervous system [84, 85].

Di- or triamines can be synthesized by the reaction of alkene moieties of diallyl-ethers, diallyl-silanes, or diallyl-amines. The reaction is carried out with $[Rh_2(-\mu\text{-}Cl)_2(COD)_2]$ catalyst at 120°C and 100 bar CO/H_2 (1:1) [86]. The non-substituted allyl systems afford mixtures of n/n, n/iso, and iso/iso products with morpholine. The n/iso ratio values range from 66:34 to 28:72 depending on the heteroatom present. On the contrary, the bis(methallyl) compounds only give the n/n products, the yields being 93%, 59%, 55%, and 66% with $–Si(CH_3)_2$, –O–, $–O(CH_2)_2O–$, –NAc groups, respectively (Scheme 28). The di- or triamines characterized by linear carbon chain between the two nitrogen atoms possess a potential biological activity [86].

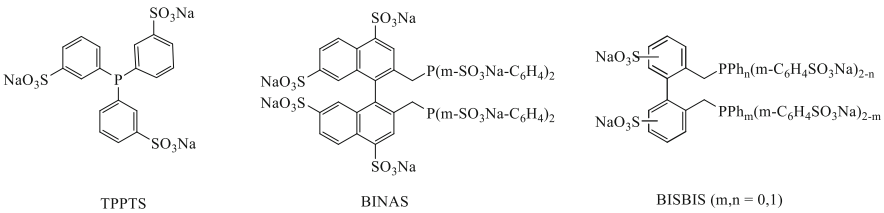


Scheme 29 Hydroaminomethylation reaction of the 1,4-bis(2-methyl-allyloxy)-benzene with *N*, *N*′-dibenzyl-butane ($n = 3$)- or hexane-($n = 5$)-1,4-diamine (adapted from ref [88])

Oxa-and azamacroheterocyclic systems are of interest for various applications due to their selective binding properties toward ions and neutral molecules and as valuable building blocks for the synthesis of natural products. Azamacroheterocyclic compounds are synthesized starting from ready available dialkenes and diamines via ring-closing bis(hydroaminomethylation) reaction [87]. This method allows for wide variations in ring size, heteroatoms, and substitution patterns to obtain various macroheterocycles. Moreover, starting from N-benzyl-substituted systems, the synthesis of cryptands can be accomplished by subsequent hydrogenolysis of the benzyl group and successive hydroaminomethylation with α,ω-dialkenes. The application of this procedure in the synthesis of azamacroheterocycles containing hydroquinone, 1,1′-biphenyl, or (*S*)-1,1′-binaphtol units is successfully conducted since relatively high yields (59–78%) are obtained [88]. The reaction involves bis-methylallylphenyl ethers and N-benzyl-diamine units (Scheme 29).

Due to the generation of two new stereogenic centers, the final products are obtained as a mixture of enantiomers and diastereomers difficult to separate [88]. These azamacrocycles can be considered as ligands for asymmetric catalysis starting from tartaric acid as the chiral unit functionalized by two methylallyl moieties, which are directly involved in the HAM reaction using diamines [89]. But this procedure is less efficient than the stepwise hydroformylation-reductive amination sequence as only 32% of the 1:1 mixture of the azamacrocycle diastereoisomers are obtained in comparison with 86% in the second process.

Intramolecular HAM also provides a direct access to synthesize azaheterocycles. A novel air stable phosphine-free ionic rhodium catalyst designed by addition of the *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) ligand affords the cationic $[Rh(CO)_2(TMEDA)]^+$ species associated to the anionic $[RhCl_2(CO)_2]^-$ moiety under CO atmosphere. The 2-isopropenylaniline is transformed into 1,2,3,4-tetrahydroquinoline with total chemoselectivity and 98% selectivity after optimization of the conditions (68 bar of CO/H_2 1:1, 100°C for 48 h). This catalytic system is extended to other 2-isopropenylanilines substituted at the nitrogen atom and in the aromatic ring. The corresponding 1,2,3,4-tetrahydroquinolines are obtained in the range of 70–98% isolated yields [90]. Similarly, these ionic diamine rhodium complexes can give 2,3,4,5-tetrahydro-1*H*-2-benzazepines starting from 2-allylaniline derivatives. In this case a more sterically demanding diamine complex obtained by the combined system of $[Rh_2(\mu\text{-}Cl)_2(COD)_2]$ with *N*,*N*,*N*′,*N*′-tetra (isopropyl)ethylene diamine (TIPEDA) or *N*,*N*,*N*′,*N*′-tetra(*o*-methylbenzyl)



Scheme 30 Representation of three sulfonated phosphine ligands

ethylene diamine (MTBEDA) is needed to improve the selectivity of the reaction. The isolated yield of each product does not exceed up to 50%, depending of the nature of the 2-allylaniline [91].

Dendritic amines with neutral core structure and amine functionalities only on the periphery of the dendrimer can present interesting potential biomedical applications, especially for DNA delivery. Starting from a dendritic polyallylether obtained by allylation of hyperbranched polyglycerol [92, 93] and the morpholine-modified polyglycerol, the dendritic polyamine is obtained with a 93:7 n/iso regioselectivity, isolated in pure form after simple dialysis with an excellent 99% yield [94]. However, to obtain this high n/iso ratio, it is necessary to operate in a sequential manner: first the hydroformylation reaction at 30 bar of CO/H_2 (1:1) in toluene with the $[Rh(acac)(CO)_2]$/Xantphos catalytic system at 70°C for 5 days and then the hydrogenation reaction after addition of morpholine at 70 bar of CO/H_2 (1:6), at 85°C for 5 days. In fact, the one-pot HAM reaction only leads to a 50:50 n/iso ratio, presumably due to the coordination of morpholine to the rhodium catalyst, which affects the regioselectivity during the hydroformylation step.

Performing the HAM reaction in an aqueous two-phase system is an elegant approach to separate the catalyst from the organic products. Experiments performed with the TPPTS monophosphine (tris-sulfonated triphenylphosphine) or BINAS diphosphine ligands (Scheme 30) lead to attractive results, with high P/Rh ratio (425 and 140, respectively) kept to maintain the $[Rh(H)(CO)L_2]$ species in the aqueous phase. However, the hydrogenation rate is significantly reduced [95]. This methodology can be extended to longer chain alkenes with dimethylamine, provided the CTAB (cetyltrimethylammonium bromide) cationic surfactant is introduced to increase the interfacial area between the two phases [96]. Indeed, in absence of CTAB, $[RhCl(CO)(TPPTS)_2]$ with an excess of TPPTS (TPPTS/Rh = 32:1) converts 67% of dodec-1-ene into 17.4% C13 amines (n/iso = 86:14) with large quantities of dodecane, internal dodecenes, and aldehydes as by-products at 130°C and 30 bar ($CO/H_2 = 1:1$) for 6 h. Introduction of CTAB (CTAB/Rh = 5.5:1) leads to 80% conversion and 51% in C13 amines (n/iso = 88:12). Addition of the BISBIS ligand (Scheme 30) to the $[RhCl(CO)(TPPTS)_2]$ complex (7.5:1 molar ratio) increases both conversion to 97% and amine chemoselectivity to 82% with high 99:1 regioselectivity. Presumably, the [RhH(CO)(BISBIS)] active species is formed to catalyze the reaction. Under the same catalytic conditions for a

BISBIS/[RhCl(CO)$(TPPTS)_2$] 5:1 ratio, hex-1-ene, oct-1-ene, dec-1-ene or tetradec-1-ene give similar high conversion rates (99.7–96.5%), high chemoselectivity (84.4–70.8%), and regioselectivity as well (97:3–99:1). Under similar conditions, dodec-1-ene reacts with diethylamine, dipropylamine, morpholine, and piperidine [97].

Addition of an acid has a positive effect on the rhodium [Rh_2(μ-Cl)$_2(COD)_2$]/TPPTS system, presumably due to the formation of a cationic [H-RhLn]$^+$ species suitable for the highly selective hydrogenation of imines and enamines [98]. The catalytic activity is not directly function of the p*K*a value but rather the size of the associated anion. It is exemplified by good performances in the reaction of oct-1-ene with morpholine, either for the conversion (99%), the selectivity in amine (85–98%) provided sulfate, acetate, trifluoroacetate, methanesulfonate, p-toluenesulfonate, sulfosuccinate or even citrate anions are present. The reaction conditions [Rh_2(μ-Cl)$_2(COD)_2$]/TPPTS (1/64), 60 bar ($CO/H_2 = 1:3$), and 130°C for 4 h have been extended to the reaction of oct-1-ene with piperidine, di-n-butylamine, and n-propylamine with similar good results and more modest performances with diisopropylamine, ethanolamine, and isopropylamine [98].

Internal alkenes are less reactive than the corresponding terminal alkenes, giving a mixture of branched amines and aldol condensation by-products due to the basic conditions. In the literature all the efforts have been devoted to combine both isomerization and hydroformylation toward the linear aldehyde (see Part 2: Isomerization-Hydroformylation) in order to selectively produce the linear amine. This goal can be achieved by using crowded diphosphine ligands such as derivatives of Naphos (Scheme 5) [99]. Thus, starting from piperidine and but-2-ene, pent-2-ene, hex-2-ene, and oct-2-ene, excellent yields and selectivities to the corresponding linear amines are reached at 120°C, under 60 bar pressure ($CO/H_2 = 1:5$) in toluene/THF mixture, after 16 h, in presence of the [$Rh(COD)_2$]BF_4/Naphos system. Selectivity in amines ranges from 91 to 98% and linear amines from 78:22 to 94:6 n/iso ratios. The results from hex-3-ene are a little bit lower with values reaching 96% and 71:29. These performances can be improved by using the t-Bu-Xantphenoxaphos ligand since, under slightly different conditions ($p_{CO} = 5$ bar, $p_{H2} = 33$ bar, 125°C, in methanol/toluene, 16 h), 99% and 96:4 values are obtained [100]. Functionalized internal alkenes have been also examined. The presence of the CN electron-withdrawing group reduces the conversion (60%), the yield in amine (45%), and the regioselectivity in linear amine to 75:25. Conversely, the OMe electron-donating substituent leads to satisfactory results such as 95%, 84%, and 93:7, respectively [100].

Another strategy to convert cyclopentene relies on the synthesis of rhodium diphosphinite complexes anchored on polyethylene glycol (PEG). High amine selectivities with morpholine and other amines are obtained at 120°C and 28 bar CO/H_2 (1:2). After addition of hexane at room temperature, the lower PEG phase containing the rhodium catalyst can be separated from the (toluene/hexane/amine) phase. Five recycling steps show that the catalytic activity is maintained [101]. The efficient rhodium diphosphinite complex described above (Scheme 12) [102] catalyzes the reaction of cyclopentene, cyclohexene, and norbornene with high activity

and selectivity close to 99%. This catalytic system also gives good performances with linear terminal alkenes and primary or secondary amines [102].

6.2 Hydroaminomethylation of Arylalkenes

Arylethylamines represent an attracting goal because they are known to exhibit a pharmacological activity. Styrene and its derivatives offer an easy access to this class of compounds. The presence of the aromatic ring provides a trend to favor the branched isomer. High temperatures and pressures bring mainly this isomer as observed at 110°C and 110 bar with phosphine-free ligand $[Rh_2(\mu\text{-}Cl)_2(COD)_2]$ (6:94 n/iso ratio) [103]. 2-Vinylnaphtalene is also transformed into the corresponding secondary or tertiary amines with the same performances [104]. Interestingly, milder conditions, 80°C and 14 bar, are required to transform styrene and various *para*-substituted styrenes into the branched isopropylamine-derived products in the ratio up to 8:92 with the zwitterionic complex $[Rh^+(COD)(\eta^6\text{-}PhBPh_3)^-]$ [105]. The reaction can be applied to both primary and secondary amines keeping good ratios in branched amines provided the CO/H_2 pressure is increased up to 68 bar.

The presence of phosphine ligands allows operation under mild conditions (60°C, 30 bar $CO/H_2 = 1{:}5$) as illustrated with the cationic active species generated from $[Rh(COD)_2]BF_4$/Xantphos or 1,1′-bis(diphenylphosphino)ferrocene, providing 15:85 or 12:88 n/iso regioselectivity, respectively [106]. The addition of HBF_4 is crucial to gain high yields in amines. Similar results are obtained in presence of the (*o*-diphenylphosphino-[N-(2-hydroxyethyl)-N-methyl]aniline) P,N bidentate ligand although it is necessary to operate at 80°C and 100 bar [107]. Another interesting study to reach high regioselectivity in the branched amine is related to the use of a sol–gel immobilized rhodium catalyst for the functionalization of some vinylarenes with aniline or nitrobenzene derivatives in an aqueous microemulsion [108]. A slight influence of the electronic nature of the substrates on the regioselectivity is observed. For example, the HAM of 4-chlorostyrene with aniline affords a ratio of n/iso = 2:98 instead of 6:94 with 4-methylstyrene. Ortho-substituted substrates can affect the regioselectivity due to their steric hindrance. Indeed, 2-chlorostyrene gives only a 9:91 ratio compared to 4-chlorostyrene with 2:98. This latter result can also be reached with nitrobenzene in a one-pot procedure over the course of the reaction. However, either electron-donating or electron-withdrawing substituents in *para*-position of aniline, or nitrobenzene, decrease the performance in terms of the yields (79–82% instead of 91%) and the regioselectivity in the branched isomer (n/iso = 13:87 instead of 2:98).

In a reverse strategy to reach highly linear-selective HAM of styrene, the very crowded tetraphosphine ligands (Scheme 7) are used. Starting from styrene and piperidine, the corresponding amine is obtained in a 94:6 n/iso ratio at 125°C and 40 bar ($CO/H_2 = 3{:}1$) in the polar *tert*-amyl alcohol solvent. To obtain such

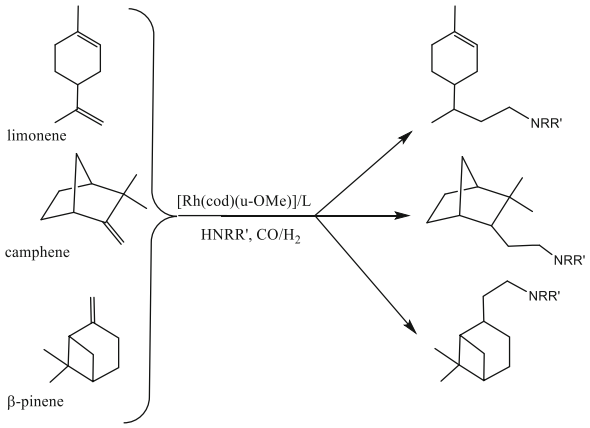
performances, the partial CO pressure needs to be high in the CO/H_2 gas mixture [109].

As expected from the Keulemans rule for the hydroformylation step [110], the condensation of piperidine to 1,1-diphenylethene (or 1-phenyl-styrene) exclusively gives the linear 3,3-diphenylamines, which constitute the basic backbone in many biological compounds like fenpiprane, diisoproamine, and prozapine. Using the [RhCl(COD)(Imes)] catalytic system (Imes being the 1,3-dimesitylimidazol-2-ylidene ligand), 99% selectivity is obtained at 125°C and 60 bar ($CO/H_2 = 1:5$) in toluene [111]. The same catalyst transforms under similar conditions α-methylstyrene into the corresponding linear piperidine-amine with >99:1 regioselectivity, whereas styrene gives rise to lower 21:79 regioselectivity [112]. Extension of the reaction to allylbenzenes provides good activity and n/iso selectivity of 88:12 [113] and 90:10 [114].

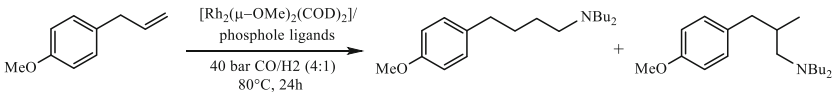
6.3 *Hydroaminomethylation of Monoterpenes and Fatty Acids*

This HAM reaction is a powerful method to functionalize renewable substrates. Limonene is one of the major constituents of the essential oil extracted from citric plants [115]. It can be transformed with secondary amines like diethylamine and morpholine in 81–93% yields and gives exclusively the linear product, owing to the steric hindrance of the isopropenyl group [116]. The catalytic conditions are 80 bar of CO/H_2 (1:1), 80°C, and 20 h in presence of the dimer $[Rh_2(\mu\text{-}Cl)_2(COD)_2]$ catalyst. The reaction gives an easy access to growth regulators for tobacco plants.

Seven other (*R*)-(+)-limonene-derived amines have been synthesized in good isolated yields [117]. Alkylated amines (n-propylamine, isopropylamine, benzylamine), cyclic amines (piperidine, piperazine, morpholine), and an aromatic one (aniline) have been used. In order to decrease the long reaction time for completion (sometimes 48 h), it is possible to improve the HAM protocol in splitting the process into two steps: hydroformylation (under a CO/H_2 mixture) and hydrogenation (only H_2). Depending on the amine used as substrate, the total reaction time is between 10 and 24 h. Higher selectivity is reached for the products of the reactions with secondary amines (79–89% isolated yield). The products were tested against *Leishmania (V) braziliensis* and some of them (the resulting amines from n-propylamine and aniline) demonstrated higher in vitro activity than the standard drug pentamidine. Two promising new *anti-Trypanosoma cruzi* limonene derivatives have also been identified (the resulting amines from aniline and piperazine) [118]. With the goal to transform natural products that can be extracted from renewable crops in large amounts into useful or potentially useful new chemicals, the HAM of limonene, camphene, α-pinene [119], and eugenol [120] has been carried out in presence of di-n-butylamine, morpholine, and n-butylamine to obtain the corresponding homologous amines. Moderate to good yields (73–94%) are



Scheme 31 Hydroaminomethylation of limonene, camphene, and α-pinene (from Ref. [119])

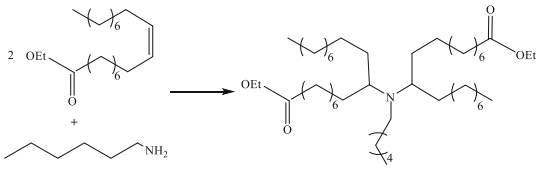


Scheme 32 HAM reaction of estragole (from Ref. [122])

reached using $[Rh_2(\mu\text{-}OMe)_2(COD)_2]$ as catalytic precursor in the presence or not of phosphines as ancillary ligands in toluene at 80°C under 60 bar of CO/H_2 pressure. The regioselectivity of the reaction is strongly induced by the substrate itself and the amine group is almost exclusively present in the α-carbon position (Scheme 31).

The rhodium catalyst in absence of ligands is very efficient for the HAM transformation of terpenes, notably camphene in which double bond isomerization is not a competitive reaction. The addition of the triphenylphosphine ligand can prevent isomerization but decreases the enamine/imine hydrogenation rate. Bulkier tribenzylphosphine at appropriate concentration gives better results due probably to its greater steric hindrance which disfavors the formation of the bis-ligand-metal species $[Rh(H)(CO)_2L_2]$ less active in the reaction [119]. All the products formed, except the final amine obtained from limonene and morpholine, are new, and the products derived from limonene have potential bioactivity.

The HAM of estragole, a bio-renewable starting material available from basil oil (90% of estragole), is reported using di-n-butylamine as the amine counterpart. The corresponding phenylalkylamines which can present fungicidal activities [121] are obtained in good yields (80–87%) (Scheme 32). The monophospholes are good candidates as ancillaries for the HAM, and they are a promising option because they have been more efficient in promoting the reductive amination than the classic PPh_3 ligand and resulted in less side products than the systems with phosphites [122].



Scheme 33 Double HAM involving ethyl oleate and hexylamine (from Refs. [123] and [124])

Hydrolysis of fats and oils gives rise to even-numbered aliphatic carboxylic acids and coproduces glycerol. The C18 oleic acid is widely produced from many crops.

The HAM of ethyl oleate has been recently explored with hexylamine, benzylamine, aspartic acid diethyl ester, valinol, and morpholine [123]. The reaction proceeds in toluene or 1,4-dioxane at 140°C for 20 h under a 100 bar CO/H_2 pressure in the presence of $[Rh_2(\mu\text{-}Cl)_2(COD)_2]$ precatalyst. High yields can be obtained, such as 99% with morpholine. However, diisopropylamine gives mainly the aldehyde and only 5% of the amine, since the hydrogenation step converts the two aldehyde regioisomers into the corresponding alcohols. Interestingly, two equivalents of oleic ester with the primary hexylamine results in the formation of the tertiary amine after a double hydroaminoamination reaction (Scheme 33) [123, 124].

An extension of this reaction using *S*(−) or *R*(+)-pyrrolidine-2-carboxylic acid or proline in methanol allows to combine the HAM reaction with an esterification giving rise to a diester, an interesting biopolymer precursor. Thermomorphic solvent systems involving linear alkanes as the second solvent result in yields as high as 95% in the two expected regioisomers and the separation of the catalyst with a leaching reduced to several ppm [125, 126]. Similarly, oleyl alcohol is transformed with diethylamine and the resulting amino alcohol separated in a thermomorphic process [127].

7 Conclusion

This chapter presents the recent advances in the tandem rhodium carbonylation reactions involving in the main step the hydroformylation. Such reactions open huge opportunities in synthetic chemistry. Indeed, they offer a general efficient strategy to synthesize building blocks for fine chemistry, starting from abundant and low price substrates and avoiding the formation of substantial amounts of by-products. This atom-efficient tandem reaction approach shows that rhodium has a privileged place in the CO chemistry, not only to perform the hydroformylation reaction but also to combine it with other functionalization processes.

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