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Maurizio Taddei
André Mann *Editors*

Hydroformylation for Organic Synthesis

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Aims and Scope

The series Topics in Current Chemistry presents critical reviews of the present and future trends in modern chemical research. The scope of coverage includes all areas of chemical science including the interfaces with related disciplines such as biology, medicine and materials science.

The goal of each thematic volume is to give the non-specialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights are emerging that are of interest to larger scientific audience.

Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5 to 10 years should be presented. A description of the laboratory procedures involved is often useful to the reader. The coverage should not be exhaustive in data, but should rather be conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

Discussion of possible future research directions in the area is welcome.

Review articles for the individual volumes are invited by the volume editors.

Readership: research chemists at universities or in industry, graduate students.

Maurizio Taddei • André Mann
Editors

Hydroformylation for Organic Synthesis

With contributions by

R.W. Bates · H. Bricout · E. Cini · C. Claver · C. Godard · L. Gonsalvi · A. Guerriero · F. Hapiot · S. Kasinathan · E. Monflier · B.F. Perandones · M. Peruzzini · E. Petricci · R. Settambolo · S. Tilloy

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Editors
Maurizio Taddei
Dipartimento Farmaco Chimico Tecnologico
University of Siena
Siena
Italy

André Mann
Laboratoire d'Innovation Thérapeutique
CNRS-Université de STRASBOURG
Illkirch
France

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Preface

Is hydroformylation still a hot topic in 2013? Do chemists still pay attention to one of the oldest metal catalysed organic reactions? Looking today in SciFinder (July 2013) under the query "hydroformylation", more than 1,270 titles were found from 2009 to 2013, with 350 patents, 820 articles/communications and 100 titles of different origin. So the answer is yes. In the age of green chemistry, atom economy and process efficiency, hydroformylation is highly pursued in industry and academia with the objective of producing and developing molecules or materials. Consequently, it is time for a brief review of the most modern technologies associated with hydroformylation.

As hydroformylation is a metal catalysed reaction, the coverage is opened by a comprehensive review of the role of metal and ligands, the core of the process that cannot be ignored. A group of qualified inorganic chemists introduce us to the multiple choices of metals and ligands required for an optimal hydroformylation. Then, as the possibility to recycle the catalyst, simplify the purification process and reduce waste and costs are mandatory for contemporary organic synthesis, the next chapter deals with the use of biphasic media for hydroformylation. Following this, the most "organic" chapters are presented. Asymmetric hydroformylation is growing all the time and the third chapter highlights the most recent advances in the field. Hydroformylation is also one of the most versatile reactions for domino applications. Atom economy and efficiency at a glance is given in two chapters dealing with domino or multicomponent processes for the synthesis of heterocyclic compounds. At the end of the volume, the most intriguing aspect of organic synthesis, i.e. natural product synthesis, is reviewed, highlighting the role of hydroformylation with several instructive examples.

These chapters should give a taste of the high level of refinement reached nowadays by hydroformylation. We present this "old" reaction to an audience of organic chemists who may or may not be conscious of its potential for synthesis of complex molecules. However, we are sure that those who are not aware of this potential will be convinced after reading these chapters.

This volume is also our very last contribution together to the field, a fascinating reaction that has a tremendous potential in the hands of synthetic organic chemists. It is not so difficult to carry out – please don't be afraid of H_2 and CO – try hydroformylation and you'll be hooked.

André Mann and Maurizio Taddei

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The Role of Metals and Ligands in Organic Hydroformylation

Luca Gonsalvi, Antonella Guerriero, Eric Monflier, Frédéric Hapiot, and Maurizio Peruzzini

Abstract In this chapter the effect of transition metals and of ancillary stabilizing ligands on the activity, regioselectivity, and chemoselectivity in hydroformylation reactions applied to organic synthesis will be reviewed, highlighting recent cases of particular interest, including examples of both homogeneous and heterogeneous catalytic reactions.

Keywords Hydroformylation · Ligand effects · P-based ligands · Transition metals

Contents

L. Gonsalvi, A. Guerriero, and M. Peruzzini (✉)
Consiglio Nazionale delle Ricerche, Istituto di Chimica dei Composti Organometallici (ICCOM-CNR), Via Madonna del Piano 10, 50019 Sesto Fiorentino (Firenze), Italy
e-mail: maurizio.peruzzini@iccom.cnr.it

E. Monflier and F. Hapiot
Faculté Jean Perrin, Université Lille Nord de France, CNRS UMR 8181, Unité de Catalyse et de Chimie du Solide, UCCS UArtois, rue Jean Souvraz, SP18, Lens 62300, France
e-mail: frederic.hapiot@univ-artois.fr

Abbreviations

acac	Acetylacetonate
bcope	Bis(cyclooctyl)phosphinoethane
BDP	Bisdiazaphospholane
Biphephos	6,6′-[(3,3′-Di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)bis (oxy)]bis(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin)
Bisbi	2,2′-Bis-((dipheny1phosphino)methyl)-1,l′-biphenyl
Boc	*tert*-Butoxycarbonyl
BTAC	Benzyl triethylammonium chloride
COD	1,5-Cyclooctadiene
CTAC	Cetyltrimethylammonium chloride
dppb	Bis(diphenylphosphino)butane
dppe	Bis(diphenylphosphino)ethane
dppf	Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
ee	Enantiomeric excess
h	Hour(s)
HPA	Heteropolyacids
i-Pr	Isopropyl
L	Liter(s)
l/*b*	Linear to branched aldehyde ratio
MeO	Methoxy
mol	Mole(s)
NHC	*N*-Heterocyclic carbene ligand
NMP	*N*-Methylpyrrolidone
PhO	Phenoxy
s	Second(s)
Tangphos	(1*S*,1*S*′,2*R*,2*R*′)-1,1′-Di-*tert*-butyl-(2,2′)-diphospholane
t-Bu	*tert*-Butyl
TMS	Trimethylsilyl
TOF	Turnover frequency
TPPMS	(Meta-sulfonatophenyl)diphenylphosphine
TPPTS	Tris(meta-sulfonatophenyl)phosphine
Xanthphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

1 Introduction

Hydroformylation was discovered in early 1900 by Otto Roelen, who named it "oxo process." This process represents one of the largest homogeneously catalyzed reactions in industry today. During 2008 almost 10.4 million metric tons of oxo chemicals were produced. Plants operate worldwide with an output of several hundred thousand metric tons per year. Over the years, both academia and industry have invested heavily in research related to hydroformylation, and some authors have concluded that this is actually one of the most studied processes in chemistry [1]. Due to its importance and process development over the years, it is not surprising that many well known reference books related to hydroformylation are considered today as science "classics" [2–5].

The process formally consists in the addition of a CHO group to a carbon atom of an olefin, and thus involves olefins as substrate and generally a mixture of CO and H_2 gas under pressure. In order to run at operatively convenient conditions of pressures and temperatures, the reaction needs to include the presence of a catalyst, usually in the form of a transition metal precursor either dispersed on a support (heterogeneous catalyst) or more conveniently in the form of a molecular complex (homogeneous catalyst). In the latter case, research has focused over the years on the design of more and more specialized ligands, generally but not exclusively containing phosphorus as binding atom, in order to increase chemo-, regio-, and enantioselectivities of hydroformylations, leading, for example, to the fundamental concepts of "natural bite angle" which now constitutes a pre-requisite for ligand design in hydroformylation (see Sect. 3.1).

From the initial application of hydroformylation to bulk chemicals (ethene, propene, and short chain olefins) for the manufacturing of products to be used as lubricants, plasticizers, and detergents, the process has been applied, albeit often only on a laboratory scale, to the synthesis of organic chemicals to be used for many different applications such as pharmaceutical intermediates, chiral auxiliaries for synthesis, etc. Many yearly surveys [6–11] and reviews [12] have appeared in the literature summarizing these results, together with some more specific reports recently highlighting the hydroformylation of renewable resources such as fatty compounds and terpenes [13], and applications of Rh-catalyzed hydroformylation in the pharmaceutical, agrochemical, and perfume industries [14]. The industrial viewpoint on selected processes using catalytic hydroformylation in one or more synthetic steps, has been also reviewed by Chaudhari [15] and by Puckette, the latter summarizing the state-of-the-art at Eastman Co [16].

The scope of this chapter is to present recent literature examples highlighting the effects of transition metals and ligands in organic hydroformylation. Aspects linked to water phase reactions (Ruhrchemie-Rhône Poulenc technology) [17], the use of different reaction media, such as fluorous phases, supercritical (sc) CO_2, ionic liquids, etc., and tethering of active homogeneous complexes on insoluble matrices and polymers [18] are discussed elsewhere and will not be considered here.

2 Transition Metals Effect in Hydroformylation

Although the most used metals for hydroformylations are Rh and Co, which are also historically the first to be proven to give superior performances in this kind of catalytic process, most platinum group metals are known to be active in hydroformylation. The processes are generally divided into (1) "unmodified," i.e., not involving the use of ancillary ligands, historically the most dated, and (2) "modified" when phosphines, phosphites, phosphonites, etc., are used to promote specific needs such as high regio-, chemo-, and enantioselectivities. A general formula for hydroformylation catalysts is $[HM(CO)_xL_y]$, where M = transition metal and L = CO or an organic ligand (modified).

Rhodium is by far the most active metal, allowing for processes to be run under mild pressures of CO/H_2 (20–80 bar) at temperatures below 140 °C. Cobalt-based catalysts usually require higher pressures (200–350 bar) and temperatures up to 190 °C to get acceptable activities [19]. The use of other metals in the periodic table are mentioned in the literature but usually endowed with lower activity. A generally accepted scale [20] for metal activity follows the order

$$Rh \gg Co > Ir > Ru > Os \sim Tc > Pt > Pd > Mn > Fe > Ni \gg Re$$

Some metals are known to show synergistic effects when bimetallic catalysts are used. Some recent examples are summarized in Sect. 2.6.

Historically, hydroformylation was carried out in the presence of heterogeneous cobalt catalysts, but very soon further mechanistic studies showed that the active species is the homogeneous complex hydridocobaltcarbonyl $HCo(CO)_4$, stable only under CO/H_2 pressure [19]. In a similar way, in the case of (unmodified) rhodium hydroformylation catalysts, hydridotetracarbonylrhodium $HRh(CO)_4$ was demonstrated to be the active species [21]. The identification of each organometallic species taking part in the catalytic cycle of hydroformylation is still a matter of debate after many years. The development of spectroscopic in situ methods has helped to unravel some of the key aspects of this fundamental organometallic catalysis, and review articles have appeared in the literature [22–24].

Although it is not the purpose of this chapter to summarize the historical development of hydroformylation catalysts, which has been described in many textbooks, it is important to underline that one of the major developments was achieved when it was found that CO ligands in first-generation Co catalysts could be replaced efficiently by other donor ligands such as phosphines, leading to second-generation Rh-based catalysts [19]. Since then, most of the process development involved the search for more sophisticated ligand variations and design, able to solve the problems of selectivity inherent in hydroformylation. It is therefore of interest to summarize in the next sections some recent examples of metal effects (Sect. 2) and to pinpoint the state-of-the-art of ligands development in organic hydroformylation (Sect. 3).

2.1 Rhodium

Ligand-modified Rh hydroformylation catalysts are generally synthesized starting from metal precursors such as $RhCl_3 \cdot (H_2O)_x$, $Rh(OAc)_3$, Rh(II) carboxylates, $Rh(acac)(CO)_2$, Rh(acac)(COD), Rh thiolates, and $Rh_4(CO)_{12}$ in the presence of the desired ligand, often under pressure with CO/H_2 or directly in situ. $Rh(acac)(CO)_2$ is usually preferred in laboratory scale tests as it is rather stable and easy to handle. As previously stated, Rh is by far the most active metal in olefin hydroformylation, and most ligand design has involved Rh complexes and their applications. In contrast with Co, ligand-modified rhodium catalysts are more active than their unmodified metal analogues. In particular, phosphites were found to be suitable ligands in this process, being better π-acceptors than phosphines, thus facilitating CO dissociation during the catalytic cycle and giving faster reaction rates. In a similar way, less-basic phosphines produce faster reaction rates and higher linear-to-branched ratios [25].

It is worth summarizing here the most important Rh-based industrial processes and some interesting recent examples of unusual systems involving this metal.

Hydroformylation of vinyl acetate monomer (VAM) has been used as one of the key steps for the synthesis of 1,2-propanediol (1,2-PDO) and 1,3-propanediol (1,3-PDO). With $HRh(CO)(PPh_3)_3$, $Rh(CO)_2(acac)$, and $[Rh(COD)Cl]_2$ as catalyst precursors, high conversion (99%) of VAM with 99% regioselectivity for 2-acetoxypropionaldehyde (2-ACPAL) was observed at 373–383 K and 41 bar pressure of CO/H_2 at 1:1 ratio. 2-ACPAL and 3-ACPAL can be further converted to 1,2-propanediol and 1,3-propanediol by hydrogenation and hydrolysis steps with quantitative yields [26].

Another important industrial process involving hydroformylation is the synthesis of a key intermediate of vitamin-A, namely 2-methyl-4-acetoxy butenal (MAB) which can be obtained from the hydroformylation of 1,4 diacetoxy-2-butene or 1,5-diacetoxy-2-butene. Two competing approaches were developed at BASF and Hoffman La Roche, using the former or the latter substrates, respectively. The selectivity toward MAB in the BASF process was achieved by using an unmodified rhodium carbonyl catalyst at a high reaction temperature, whereas La Roche's process did not show regioselectivity problems. Elimination of acetic acid and isomerization of the exo double bond yields MAB in both processes [19].

ARCO commercialized Kuraray technology [27] using allyl alcohol as substrate to obtain 1,4-butanediol by rhodium catalyzed hydroformylation and subsequent hydrogenation of intermediate 2-hydroxytetrahydrofuran. Pivotal to the efficiency and the stability of the catalyst was the addition of dppb as stabilizing ligand.

Another industrially relevant substrate for (bis)hydroformylation is 1,3-butadiene. Conjugated dienes are hydroformylated to dialdehydes with modified rhodium catalysts and with a high excess of phosphine (P:Rh = 30:1) [28]. Although the unsaturated monoaldehyde is easily obtained, in the second step there is a competion on the C═C bond between hydroformylation, hydrogenation, and isomerization [29]. Hydrogenation is prevalent with unmodified cobalt or rhodium

catalysts so that saturated monoaldehydes or monoalcohols are formed. Water-soluble catalysts have been applied to the hydroformylation of 1,3-butadiene giving *n*-pentanol by pentanal hydrogenation and 2-propylheptanol by aldol condensation and hydrogenation under mild conditions [30].

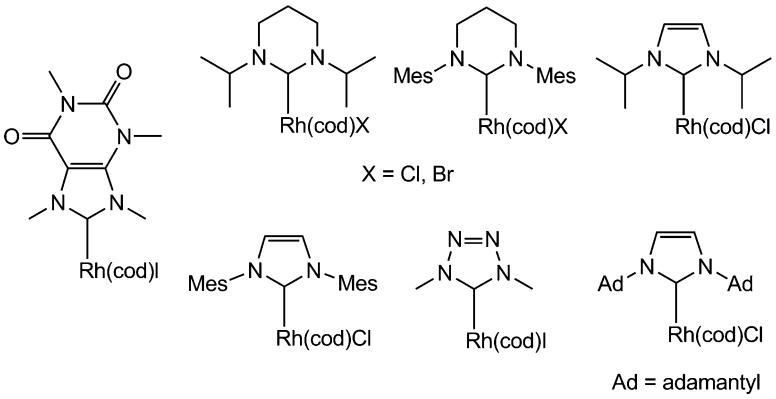
Hydroformylation of olefins using dispersed molecular catalysts on solid supports has been studied by many authors. Chaudhari and coworkers showed that co-precipitation of the water-soluble Rh complex $[HRh(CO)(TPPTS)_3]$ with Ca, Sr, or Ba nitrates on active carbon gave active catalysts for 1-decene hydroformylation at 100 °C and 41 bar syngas pressure in toluene, with a conversion of 95.1% and aldehyde yield of 89.5%. Other substrates such as 1-hexene, 1-octene, 1-dodecene, styrene, camphene, VAM, and cyclohexene were also converted chemoselectively to the corresponding aldehydes in a short time (1.8–6.4 h). The best TOF = 1,578 h^{-1} was reached with styrene. This method allows for performances comparable to the water-phase system but without the need for phase-transfer agents, with a broad range of applications for lipophilic substrates and very high recycling ability (1-decene was used as substrate for five cycles without loss of activity) [31].

Rh-catalyzed asymmetric hydroformylations became competitive with Pt–Sn-based processes after the discovery of enantiopure ligands, especially phosphine–phosphites and phosphoramidates [19]. Some examples of these ligands applied in organic hydroformylations are summarized in Sect. 3.3.

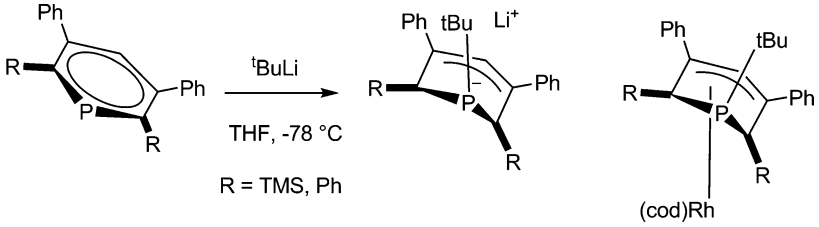
One of the challenges of Rh-catalyzed hydroformylation is to obtain C_9-aldehydes from mixtures of isomeric octenes. These aldehydes are raw materials for diiso-nonyl phthalate (DINP), a high performance plasticizer. De and coworkers have studied the effect of inorganic ammonium salts such as ammonium chromate, ammonium dichromate, ammonium molybdate, and ammonium tungstate as additives for hydroformylations of C_8-olefins and 1-dodecene using $[Rh(CH_3CO_2)_2]_2$ at 80 bar syngas pressure and 140 °C, in 7:1 salt:Rh ratio. It was observed that addition of such salts could increase the yield of aldehydes without the need for phosphine oxides or phosphine ligands, also decreasing Rh loss in the distillation process for the separation of the products from the catalyst, showing that catalyst recycling was also possible [32].

Among non-phosphorus-based homogeneous Rh catalysts it is worth mentioning results obtained by Hermann, Weberskirch, and coworkers who showed that Rh-NHC complexes can be very active catalysts in the hydroformylation of 1-octene in toluene at 100 °C under syngas at a pressure of 50 bar, reaching a TOF = 3,500 h^{-1}. The major drawback of the system resided in the low regioselectivities, which were quite high at the beginning of the reaction ranging from 1.5 to 2.5 but were rapidly dropping with increasing conversions [33]. The complexes used are shown in Scheme 1.

An even more exotic series of P-ligands which did not use phosphorus as donor atom, but coordinated as η^5-ligands, are λ^4-phosphinines, which were prepared by Le Floch and coworkers by reaction of 2,6-bis(trimethylsilyl)-4,5-diphenylphosphinine and 2,3,5,6-tetraphenylphosphinine with *tert*-butyllithium. The anionic



Scheme 1 Rh-NHC complexes used in 1-octene hydroformylation



Scheme 2 Rh-phosphinidine complexes used in hydroformylation

ligand was reacted with $[Rh(cod)Cl]_2$ to yield the corresponding η^5-Rh(I) neutral complexes (Scheme 2) [34].

The catalytic activity of these complexes was tested using styrene, cyclohexene, and 2,3-dimethylbut-2-ene as substrates. Under mild conditions (syngas 20 bar, 40 °C) styrene gave high conversions and high *b*/*l* ratio (93:7) whereas cyclohexene was converted (62.2% conversion, 4 h) at very low catalysts loading (0.024%) reaching a TOF = 648 h^{-1}.

Active catalytic systems for the regioselective hydroformylation of styrene and 1-octene and substituted derivatives was obtained using $Rh_6(CO)_{16}$ in the presence of Keggin-type HPA. The effects of the nature of HPA used was studied and the best results were observed in the presence of $H_3PW_{12}O_{40}{\cdot}25H_2O$ (HPA-W12). The major issue with alkyl terminal alkenes hydroformylation was still linked to poor *l*/*b* ratio and isomerization [35].

Rh(0) nanoparticles (NPs) were also shown to be active in solventless hydroformylation of olefins [36]. Ligand-modified or unmodified NPs were prepared in imidazolium ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoborate by hydrogen reduction and showed an average diameter of 4.6–5.0 nm. Hydroformylation tests were run under 50 bar syngas pressure at 100 °C using 1-hexene, 1-octene, and 1-decene as substrates. Although a clear dependence on the size of the

NPs was determined, induction periods were invariably observed; thus the authors could not unequivocally discriminate on the amount of NP-based activity vs formation of soluble Rh carbonyl complexes under the conditions applied. More recently, Wang and coauthors reported on the efficient use of Rh NPs in a thermoregulated process based on biphasic ionic liquid/organic phase composed of *N*,*N*-dimethyl-*N*(2-(2-methoxyethoxy)ethyl) ammonium methanesulfonate/cyclohexane. Various olefins were completely converted with chemoselectivities to aldehydes higher than 98%, at 120 °C under 50 bar of syngas, with the possibility to recycle efficiently the catalyst by simple phase separation for up to five times without loss of activity [37].

2.2 Cobalt

After the initial use of the Roelen's process (first generation), initially the second generation hydroformylation catalysts used an unmodified homogeneous Co catalyst under harsh conditions. With these processes, aldehydes were produced in up to 300 kton/year, especially dialkyl phthalates. The main issue with unmodified Co catalysts in reactions such as propene hydroformylation was the low *l*/*b* ratio in the butyraldehyde product. The use of monodentate phosphine ligands helped to improve on this aspect, although in turn decreased the activity of the catalysts and promoted isomerization and hydrogenation competing pathways. In spite of this, as the reactions required in this way a temperature range of 120–190 °C and a syngas pressure of 40–300 bar, some companies, such as BASF, Sasol, and Shell, still used cobalt catalyzed hydroformylation for the production of high-boiling aldehydes or alcohols from long-chain and branched olefins. One of the technological issues linked to the use of cobalt in hydroformylation plants is its deposition as carbonyl clusters, metal, or carbides with negative influence on plant efficiency and safety (decobalting) [19].

Ligand-modified Co catalysts are usually obtained by mixing $Co_2(CO)_8$ with an excess of the phosphorus-based ligand (P) to produce salts of general formulas $[Co(CO)_4]^+[Co(CO)_3P_2]^-$, which are then converted at high temperatures into the dimers $[Co_2(CO)_6P_2]$ and finally to the active precatalysts $[HCo(CO)_3P]$ in the presence of H_2 or syngas. The mechanism of cobalt-catalyzed olefin hydroformylation has been recently reviewed [22]. Among phosphorus compounds that can be used as stabilizing ligands only alkyl phosphines are utilized in Co-based processes. The reason is due to the activity of Co complexes as hydrogenation catalysts; the aldehydes produced are often further reduced to alcohols which may react with P–O or P–N bonds in ligands, leading to deactivation through decoordination from the metal. Particularly good catalytic properties are exhibited by a class of bicyclic phosphine ligands known as phobanes (9-phosphabicyclononanes) introduced by Shell [38]. Hydrogenolysis of cobalt acyl complexes $[Co(CO)_3(L)(COR)]$ (L = phosphine, R = Me, ^{n}Pr), have recently been sudied using in situ IR spectroscopy at moderate temperatures (<75 °C) and pressures (<25 bar).

The reactions provide a model for the product-formation step in phosphine-modified, cobalt-catalyzed hydroformylation [39].

As Rh catalysts suffer from poor stability at high temperatures, most processes involving the hydroformylation of long-chain aldehydes ($>C_{10}$) still use Co catalysts, either unmodified (generally at 300 bar, 200 °C) or ligand-modified allowing for lower CO/H_2 pressures (<100 bar), reaching high selectivities toward linear alcohols, used for the production of surfactants. Hydroformylation of 1-dodecene has been carried out at Sasol with a Co catalyst in the presence of phosphabicyclononane running the process at 85 bar ($CO/H_2 = 1/2$) and 120 °C with a Co/P ratio of 1:2, obtaining C_{13}-alcohols in ca. 55% yield [40].

An important application of Co catalysts is in the hydroformylation of fatty compounds, which are a class of renewable substrates which is receiving growing attention. In the case of internal C═C bonds such as in methyl oleate, more forcing conditions are required compared to terminal olefins; hence cobalt catalysts are preferred as more resistent at higher temperatures than their rhodium analogues. Unsaturated fatty esters and vegetable oils were hydroformylated with H_2 and CO (3,500–4,600 psi) and $Co_2(CO)_8$ to give fatty aldehydes at 100–110 °C and fatty alcohols at 175–190 °C. C_{19} oxo products were obtained with varying yields ranging from 42% to 84%. The proportion of linear isomers increased at higher reaction temperatures and in the presence of tributylphosphine as stabilizing ligand [41].

Ligands other than phosphines have been used on a laboratory scale. In a comparative study, the catalytic activities of the complexes of Pd, Ru, Co, and Rh with PPh_3, $AsPh_3$, and $SbPh_3$ ligands have been investigated for the hydroformylation of ethylene under 60–80 bar of CO/H_2 gas mixture at 150 °C. All the studied metal complexes, other than Rh, with $AsPh_3$ ligand were found to show better hydroformylation catalytic activity than those of their corresponding complexes with PPh_3 and $SbPh_3$ ligands. In the case of Co, at 80 °C using a ratio Co:ligand = 1:60, conversions of ethylene were measured as 57%, 20%, and 15% after 12 h, yielding propanal in 95%, 72%, and 44% selectivity for L = $AsPh_3$, PPh_3, and $SbPh_3$, respectively [42].

Among the many different alkyl phosphines which were tested for Co-catalyzed hydroformylations, four tertiary phosphines such as $P(CH_2CH_2CN)_3$, $P(CH_2CH_2CO_2CH_3)_3$, $P(CH_2CH_2CH_2OCH_3)_3$, and $P(CH_2CH_2CH_2OCH_2CH_3)_3$ have been synthesized and used as ligands in $Co_2(CO)_6(L)_2$ complexes and tested in the hydroformylation of hex-1-ene and propene in polar solvents including water, comparing the results with the known $Co_2(CO)_8$ and $Co_2(CO)_6(PBu_3)_2$ [43]. It was observed that high concentrations of added phosphines were needed in order to reach activities comparable to $Co_2(CO)_6(PBu_3)_2$ and avoid formation of the ligand-free pre-catalyst $HCo(CO)_4$. The best perfomance was obtained with $P(CH_2CH_2CN)_3$, reaching 100% chemoselectivity to aldehydes and ca. 80% regioselectivity to linear products.

Soluble and supported metal nanoparticles, including Co, were demonstrated to be active in olefin hydroformylation. The hydroformylation of olefin has been investigated using Co and Rh catalysts supported on active carbon (AC) under

low-pressure mild conditions (130 °C, 30 bar). Co/activated carbon catalysts showed excellent catalytic performance in alcohols as solvents, while Rh/activated carbon catalyst exhibited good activity in nonpolar solvents. In EtOH, Co/AC gave 72.9 conversion of 1-hexene and 80.0% was reached in 2-propanol at 10% Co loading, yielding mixtures of aldehydes and acetals coming from condensation with alcohols. Rh/AC (1% loading) gave ca. 94% conversion of the same substrate in *n*-octane, with a maximum yield of 56.8% in heptanal [44].

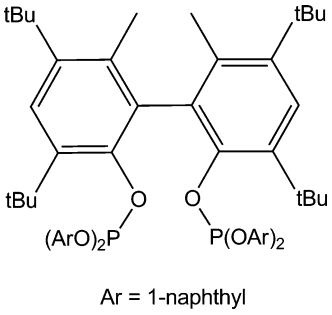
The catalytic activity of an amorphous Co–B catalyst was evaluated showing a relatively high activity (ca. 90% conversion) in the hydroformylation of 1-octene, with good selectivity (96%) to nonanal, under the conditions of Co/substrate molar ratio = 0.096, 120 °C, 80 bar, and 150 min, and the catalyst could be recycled without loss of activity after four cycles. When Co–B was supported on SiO_2, the activity of the catalyst increased. At 120 °C, 50 bar, and 2.5 h, fresh Co–B showed 71.1% conversion and 70.2% C_9-aldehyde yield (98.7% C_9-aldehyde selectivity) while Co–B/SiO_2 showed 88.3% conversion and 86.1% C_9-aldehyde yield (97.5% C_9-aldehyde selectivity). Compared with conventional supported Co catalysts, Co–B/SiO_2 showed much higher activity than Co/SiO_2 [45].

The size of Co nanoparticles has an effect on the hydroformylation performance. A new method was developed to obtain ultrafine cobalt nanoparticles (2.8 nm) from larger precursors (ca. 20 nm) using $NaBH_4$ as reducing agent. The obtained ultrafine nanoparticles showed a narrow size distribution and a much higher Co/B ratio (100 times) than that of cobalt nanoparticles precursors. The cobalt nanoparticles were used to catalyze the hydroformylation of 1-hexene at 100 °C and 24 bar, reaching an average TOF of 130 h^{-1}. Using the mercury poisoning experiments it was demonstrated that a heterogeneous catalysis mechanism was active [46].

2.3 Ruthenium

Although not one of the most active transition metals tested for catalytic hydroformylations, ruthenium has been investigated for such purpose by a few authors. Süss-Fink and Reiner studied the behavior of the trinuclear cluster anion $[HRu_3(CO)_{11}]^-$ in hydroformylation, hydrogenation, silacarbonylation, and hydrosilylation reactions. Ethylene and propylene were hydroformylated with CO and H_2 to give the corresponding aldehydes and in the case of propylene a high yield of the linear butyraldehyde was obtained [47]. Later on the study was extended and the chemo- and regioselectivity of the hydroformylation of propylene catalyzed by $[NEt_4][HRu_3(CO)_{11}]$ was studied as a function of solvent, temperature, and pressure. The catalyst was found to be highly chemoselective to aldehydes, while the regioselectivity could be optimized by proper choice of the reaction conditions, with the highest *l*/*b* ratio of 98.6:1.4 for butanal obtained [48]. Variations on this method were reported by Knifton using Ru catalysts in fused Bu_4PBr [49], and Tanaka using $PPN^+[HRu(CO)_4]^-$ and $PPN^+[HRu_3(CO)_{11}]^-$ for the hydroformylation of 1-pentene at high syngas pressure (300 bar) [50].

Scheme 3 Nozaki's A4N3 ligand



Another report by Mitsudo et al. demonstrated that a system based on the combination of $Ru_3(CO)_{12}$ and 1,10-phenanthroline gave excellent catalytic activity for hydroformylation of terminal olefins. For example, propylene was hydroformylated under 80 atm of syngas ($CO:H_2 = 1:1$) at 120–130 °C in an amide solvent to give aldehydes in high yields (65–93%) with high regioselectivity (*n*-selectivity = 95%). In the case of 1-octene, the corresponding C_9-aldehydes were obtained in moderate yields (49–55%) with high linearity (selectivity > 95%) [51].

The water-soluble complexes $[HRu(CO)(CH_3CN)(L)_3][BF_4]$ [L = TPPMS (*meta*-sulfonatophenyl-diphenylphosphine); TPPTS (tris-*m*-sulfonato-phenylphosphine)] were used as catalyst precursors for the hydroformylation of eugenol, estragole, safrole, and *trans*-anethole under moderate conditions in biphasic media and their activities were compared to a Rh carbonyl analogue. Interestingly, the use of cetyltrimethylammonium chloride (CTAC) as phase transfer agent inhibits the isomerization reaction for estragole, safrole, and transanethole, but not for eugenol, reaching high chemoselectivities for the hydroformylation products (88–100%) using TPPMS. As expected, the most remarkable difference between the Rh and Ru systems was that, apart from eugenol, all other substrates showed sluggish conversions with Ru. Safrole and estragole only reached moderate values of 15% and 30% respectively, while *trans*-anethole (internal olefin) was converted only in traces. Higher activities were observed using TPPTS, explained by the authors as due to the higher water solubility of such ligand compare to TPPMS [52].

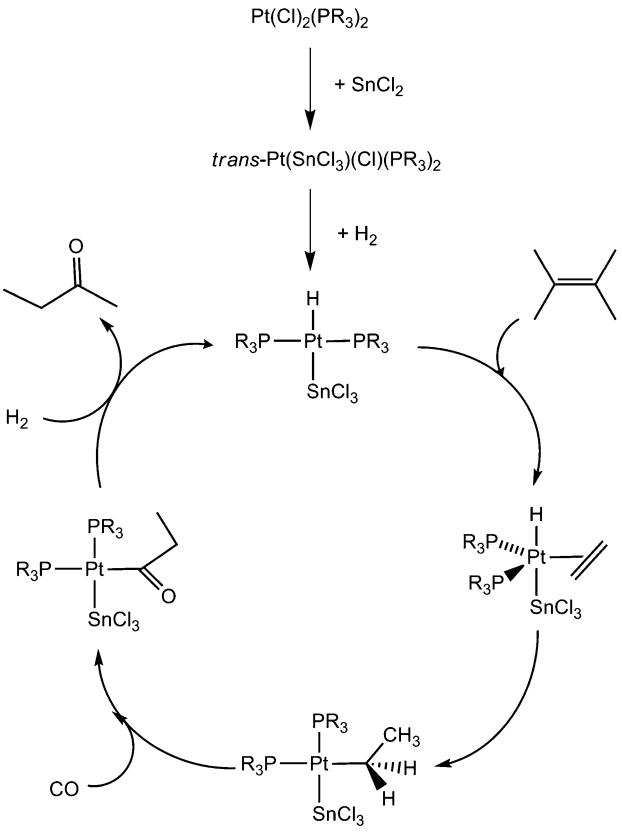
The hydroformylation of propene and 1-decene was recently studied using a combination of dimeric $[\{Cp^*Ru(acac)\}_2]$ and bidentate phosphorus ligands such as A4N3 (Scheme 3), xanthphos, and bisbi which were previously developed for rhodium hydroformylation catalysts. Other metal precursors such as $Ru_3(CO)_{12}$, $[\{(indenyl)Ru(CO)_2\}_2]$, and $[\{(1,2,3\text{-trimethylindenyl})Ru(CO)_2\}_2]$ were tested, together with the effects of temperature and ligands on *l*/*b* ratios. A remarkable *l*/*b* ratio = 79 was obtained for 1-decene hydroformylation at 100 °C, 18 h, 20 bar CO/H_2. In most cases, alkene isomerization and hydrogenation products were present to a certain extent depending on the ligands and choice or reaction conditions [53].

Ruthenium-catalyzed reactions involving at least one hydroformylation step but not involving syngas have been proposed by some authors [54]. In the presence of

Ru clusters such as $Ru_3(CO)_{12}$ or $H_4Ru_4(CO)_{12}$, a range of olefins were converted first into aldehydes then into alcohols by a hydroformylation–reduction pathway using a gas mixture of CO_2:H_2 = 1:1, generally at 80 bar overall pressure, 140 °C, 5–30 h, in the presence of halides. The study of solvent effect showed that *N*-methylpyrrolidone (NMP) gave the best results in the conversion of cyclohexene to cyclohexylmethanol [55]. Another example of the use of CO_2 instead of CO is in the hydroaminomethylation reaction, where a sequence of RWGS, olefin ($R^1CH{=}CH_2$) hydroformylation to aldehyde, aldehyde ($R^1CH_2CH_2CHO$) condensation with secondary amine to give an enamine or imine ($R^1CH{=}CHNR^2R^3$), and finally hydrogenation gives the product $R^1(CH_2)_3NR^2R^3$. The standard tests were carried out using $Ru_3(CO)_{12}$ as catalyst, toluene as solvent, LiCl as promoter, and using a mixture CO_2:H_2 = 1:3, generally at 80 bar overall pressure, 160 °C, 5 days. A variety of olefins and amines were tested, together with a screening of reaction conditions. The best yields were obtained from olefins such as cyclopentene, cyclohexene, and cyclooctene, together with morpholine in the presence of a phase transfer agent such as BTAC [56].

2.4 Platinum

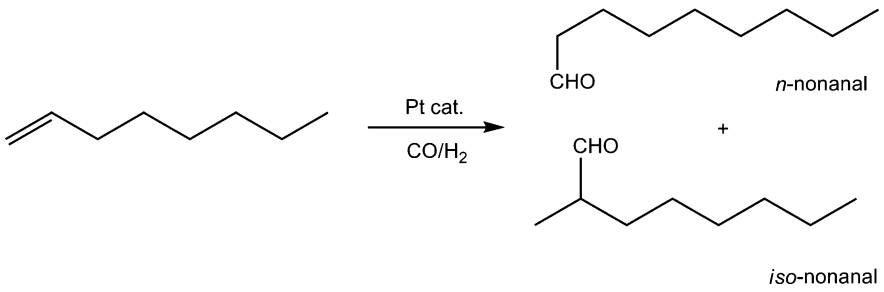
The use of platinum compounds as homogeneous catalysts has yielded numerous useful and attractive processes, including hydroformylation reactions. Whereas industrial hydroformylation processes are still run exclusively on cobalt or rhodium complexes as catalysts, platinum compounds are mainly of academic interest and advantageous to elucidate the mechanism of transition metal catalyzed reactions [57]. Indeed, ^{195}Pt is an NMR active isotope and Pt−L coupling costants give information on the nature of the bonding in a complex. Furthermore, many transient intermediates, common also to other metals, can be isolated in the case of platinum and fully characterized. In recent years, some Pt(II) complexes gave interesting results [58–60] in terms of enantioselectivity although the catalytic activity turned out to be lower compared to rhodium species. Most of the platinum complexes reported were of the type L_2PtCl_2 (L = mono- or di-phosphines) and had to be used in the presence of $SnCl_2$ to promote hydroformylation [61, 62]. The role of tin(II) chloride has been the subject of many studies and is still not completely understood. It appears that the $SnCl_3$ moiety formed by the insertion of $SnCl_2$ into the Pt−Cl bond is more labile than Cl itself and can easily be displaced promoting the interaction of the substrate with Pt [63, 64]. It has also been shown that tin(II) chloride stabilizes the formation of five coordinate platinum complexes as in the case of the $SnCl_2$ catalyzed formation of $Pt(cod)Cl_2$ [65]. The catalytic cycle of olefin hydroformylation promoted by Pt−Sn complexes has also been investigated theoretically by the group of Rocha, using the heterobimetallic *trans*-$Pt(H)(PH_3)_2(SnCl_3)$ compound as model [66] (Scheme 4). This study led to the conclusion that the hydrogenolysis process (activation energy of 22.9 kcal/mol) together with the carbonylation process (activation energy of 26.4 kcal/mol) are the lowest



Scheme 4 Proposed catalytic cycle performed by the heterobimetallic Pt–Sn catalyst [62]

energy steps of the olefin hydroformylation cycle promoted by Pt–Sn compounds. Thereafter, both processes may control the TOF of the catalyst, which is also consistent with experimental observations [67]. In addition, the Pt−Sn catalytic system showed the advantage of giving low amounts of hydrogenation products [68] and, when chiral phosphines were used as ligands, significant chemo- and diastereoselectivity ratios were achieved in asymmetric hydroformylation [69, 70].

The catalytic systems based on platinum/tin compounds also represent an alternative to the use of rhodium or cobalt complexes in the hydroformylation of inexpensive naturally occurring monoterpenes, which are of great interest for the production of aldehydes and alcohols in both the pharmaceutical and perfume industries [71]. (−)-β-Pinene, *R*-(+)-limonene, and (−)-camphene have been hydroformylated regiospecifically to the linear isomers of corresponding aldehydes by using platinum(II)/tin(II)/phosphine (or diphosphine) catalytic systems [68]. In contrast to most rhodium or cobalt compounds, the undesirable isomerization of β- to α-pinene took place rather slowly with Pt systems (1–5% based on reacted β-pinene). In the case of camphene, the highest diastereomeric excess (60%) was



Scheme 5 Products of hydroformylation of 1-octene catalyzed by Pt/($SnB_{11}H_{11}$) complexes [75]

achieved with the platinum/tin/(*R*)- or (*S*)-BINAP system with ca. 85% chemoselectivity for the linear aldehydes at ca. 90% camphene conversion [69]. The hydroformylation of myrcene with rhodium and platinum/tin catalysts bearing P-donor ligands was also studied and the major products of the reaction identified [72]. Not only phosphines but also arsine-based ligands [73] were synthesized and tested in Pt/Sn catalyzed hydroformylation of terminal alkenes [74]. These systems showed very high *l*/*b* ratios, probably due to the wide bite angle of ligands which increases the steric congestion around the metal center, resulting in more selective formation of the sterically less hindered linear aldehydes.

As a result of the comparative study on the hydroformylation activity between $SnCl_3$ and $[SnB_{11}H_{11}]^-$, the complexes $[Pt(dppp)Ph(SnB_{11}H_{11})]^-$ and $[Pt(dppp)Ph(SnB_{11}H_{11})_2]^{2-}$ were synthesized [75]. These two stanna-*closo*-dodecaborate complexes showed a higher thermal stability and turned out to be more selective in the hydroformylation of 1-octene than their $SnCl_3$ analogues, giving *n*- and *iso*-nonanal as the only aldehydes produced during catalysis (Scheme 5).

Recently some different Pt(II) triflate complexes of general formula $[P_2Pt(H_2O)_2](OTf)_2$ were prepared and tested in the hydroformylation of a variety of terminal and internal alkenes under mild conditions in an aqueous micellar medium [76]. In addition to ensuring the complete dissolution of catalyst and substrate in water, the use of surfactants permitted the separation of catalyst from the organic products and the recycle with only a modest loss of activity. Aldehydes were obtained with linear to branched ratios up to >99:1 and, in the case of styrene derivatives, the corresponding benzaldehydes were formed. Hydroformylation of styrene with platinum compounds has been extensively investigated by different research groups. The preformed catalyst $[Pt(PP_3)(SnCl_3)]SnCl_3$ (PP_3 = tris[2-(diphenylphosphino)ethyl]phosphine) showed high aldehyde selectivity (99%) under conditions of 100 °C and 100 bar CO/H_2 (1:1) pressure [77]. High chemo- and regioselectivities up to 99.8% and 88%, respectively, were also reached with a platinum-xantphos/$SnCl_2$ system in the hydroformylation of styrene [60]. In this case the catalytic system turned out to be active over a range of 25–100 °C temperatures and 120 bar of CO/H_2 = 1:1. The chiral xanthenes-based diphosphonite ligands prepared by Vogt et al. were also applied in the Pt/Sn-catalyzed asymmetric hydroformylation of styrene [78], reaching chemoselectivities of up to 75% and

Table 1 Relative activity scale of transition metals in hydroformylation reactions [12]

Metal	Rh	Co	Ir	Ru	Os	Tc	Mn	Fe	Re
Log (relative activity)	3	0	−1	−2	−3	−3	−4	−6	<−6

regioselectivities of up to 83%. Concerning enatioselectivity, an interesting inversion of the stereoselection process was observed by increasing the temperature, which was hypothesized to be due to conformational changes in the catalyst structure at elevated temperatures. Finally, among the examples of heterogeneous systems applied in hydroformylations, the use of platinum can also be found [79]. In the hydroformylation of 1-hexene, the addition of small amount of Pt (1 wt%) as promoter to 10 wt% Co/AC (AC = active carbon) catalyst improved the catalytic performance significantly, giving a 96.3% conversion and 66.6% oxygenate selectivity.

2.5 Other Metals

Despite the significant industrial interest in hydroformylation reactions, those based on metals other than rhodium or cobalt have received little interest. A generally accepted order of activity of transition metal complexes in hydroformylations is given in Table 1 [12, 20]. Moreover, by introduction of ligands and cocatalysts, the activity of a given complex can be considerably altered.

2.5.1 Palladium

The palladium complex $PdCl_2(PCy_3)_2$ turned out to be a regio- and chemoselective catalyst for the hydroformylation of internal alkynes to give the corresponding α,β-unsaturated aldehydes [80], with the best results achieved at 150 °C and 70 bar CO/H_2 = 1:1. Furthermore, the combined use of $PdCl_2(PCy_3)$ and $Co_2(CO)_8$ remarkably improved the catalytic activity, giving higher conversion in a shorter time, with little change of selectivity. Drent et al. demonstrated that catalytic systems consisting of a Pd(II) diphosphine complex in the presence of weakly or non-coordinating counterions were active in olefins hydroformylation [81]. In particular, by varying the ligand, anion, or solvent, the reaction could be steered to give alcohols, aldehydes, ketones, or oligoketones. Non-coordinating anions and arylphosphine ligands produced primarily (oligo)ketones, while increasing the ligand basicity or anion coordination strength shifted the product selectivity towards aldehydes and alcohols. Afterwards, the same research group reported another example of palladium catalyzed hydroformylation of internal alkenes to linear alcohols. The complex $[Pd(bcope)(OTf)_2]$ in the presence of substoichiometrically (with respect to Pd) added halide anions was shown to be a highly efficient homogeneous catalyst under mild reaction conditions (105 °C, 60 bar CO/H_2 1:1) [82]. The effect of the halide anions was observed in the rate as well in the chemo-

and regioselectivity of hydroformylation. Thus, the rate of hydroformylation of internal higher alkenes increased by a factor of about 6–7 in the presence of chloride/bromide and about a factor of 3–4 with iodide, while the selectivity towards alcohols increased to almost 100% upon addition of the halide anion. Notably, the regioselectivity towards linear alcohol increased in the reverse order, i.e., iodide > bromide > chloride. Hydroformylation of 1-octene has also been investigated with palladium in the presence of different phosphine ligands and acid as cocatalysts [83]. Best results were obtained with in situ generated Pd/bidentate phosphines complexes and an appropriate acid concentration. The latter turned out to be a crucial factor for achieving high linear selectivity. As mentioned above for platinum, the addition of 1 wt% of palladium to Co/AC catalyst improved the catalytic performance in the hydroformylation of 1-hexene even if the activity and selectivity were lower than those of Co/AC with Pt [79]. Instead, 89.7% conversion and 88.9% oxygenate products selectivity were obtained after 2 h reaction in the hydroformylation of 1-hexene by adding small amounts of palladium to Co/SiO_2 catalyst [84]. The addition of Pd to this system increased reduction products, promoted the metal dispersion, and minimized the particle size of cobalt, resulting in the enhancement of carbonyl adsorption at the catalyst. Finally, the catalytic behavior of Pd/SiO_2 catalysts was investigated for ethane hydroformylation [85] and, when prepared from dinitroamminepalladium, the resulting catalyst was found to show high activity, thanks to the greater dispersion of metal on the support.

2.5.2 Iridium

Among metals having shown potential catalytic activities in hydroformylation, iridium has also been considered. The hydroformylation reaction of 1-hexene was studied with some iridium complexes in the presence of inorganic salts, which played an important role in terms of the percentages of products obtained. The catalytic activity increased in the order $IrCl_3 < [IrCl(CO)_3]_n < Ir_4(CO)_{12}$ and best results were achieved by using LiCl and $CaCl_2$ as promoters [86]. Hydroformylation of 1-hexene and styrene was also performed with Ir(xantphos) hydride complexes under mild conditions, showing only a modest catalytic activity [87]. Siloxide complexes of iridium(I) [88] have been used as catalysts for hydroformylation of several vinylsilanes, giving both hydroformylation and hydrogenation products under very mild reaction conditions (80 °C, 10 bar CO/H_2 1:1).

Recently, Beller and coworkers [89] have demonstrated that iridium/phosphine complexes promote the efficient hydroformylation of a variety of olefins. By using 1-octene as the model substrate, they first studied the effects of different solvents and iridium precursors under a given set of conditions (Table 2). From these studies it was shown that [Ir(cod)(acac)] is the best metal precursor in terms of chemoselectivity and solvent also has a significant influence on the chemoselectivity of the reaction. In particular, polar solvents favored the formation of hydroformylation products over that of hydrogenation. By using [Ir(cod)(acac)] with

Table 2 Hydroformylation of 1-octene catalyzed by Ir(I) complexes in the presence of PPh_3 (2 equiv.) [89]

Entry	Ir source	Solvent	Yield (%)	*n/iso*	Hydrogenation products (%)	Isomerization products (%)
1	[Ir(cod)(acac)]	THF	58	76:24	14	2
2	[Ir(cod)(acac)]	*o*-Xylene	61	75:25	23	2
3	[Ir(cod)(acac)]	Heptane	27	68:32	61	10
4	[Ir(cod)(acac)]	Diglyme	57	75:25	17	2
5	[Ir(cod)(acac)]	Toluene	50	75:25	33	5
6	[Ir(cod)(acac)]	NMP	74	74:26	9	1
7	$[\{Ir(cod)Cl\}_2]$	THF	30	71:28	47	10
8	$[Ir(cod)_2]BF_4$	THF	42	74:26	12	12

For reaction conditions see [89]

2.2 equiv. of PPh_3 in *N*-methylpyrrolidone (NMP), hydroformylation of 1-octene gave aldehydes in 89% yield.

2.5.3 Nickel

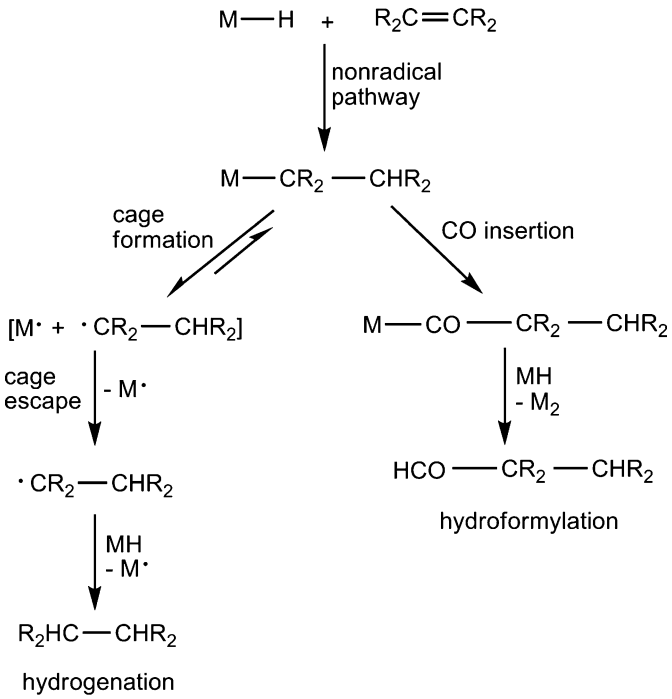
Ni/SiO_2 and its sulfide derivative $S-Ni/SiO_2$ obtained by sulfidation with H_2S have been tested as catalysts in ethylene hydroformylation [90]. Whereas adsorbed sulfur is known to poison olefin hydrogenation, sulfidation led to an increase of propionaldehyde selectivity by a factor of 3–4 at 240 °C and 1–30 atm pressures. Due to the simple formation of carbonyl $Ni(CO)_4$ from $S-Ni/SiO_2$, this catalyst has turned out not to be suitable for industrial application.

2.5.4 Manganese

One example of manganese compounds applied to the hydroformylation reaction was reported by Noyori in 1995 [91]. In this study, complex $HMn(CO)_5$ was tested in the hydroformylation of 3,3-dimethyl-1,2-diphenylcyclopropene in different solvents and the mechanism of reaction was also investigated. Identical selectivities found in hexane, neat olefin, and $scCO_2$ suggested that hydroformylation occurred by a nonradical pathway, as indicated in Scheme 6.

2.5.5 Molybdenum

The more recent molybdenum complex *mer*-$[Mo(CO)_3(p\text{-}C_5H_4N\text{-}CN)_3]$, prepared by UV-irradiation of $Mo(CO)_6$ and paracyanopyridine in THF solution [92], showed catalytic activity in hydroformylation of numerous olefins such as 1-hexene, cyclohexene, and 2,3-dimethyl-2-butene. In the case of 1-hexene, the catalyst gave a 95% conversion under moderate reaction conditions (100 °C,



Scheme 6 Proposed mechanism for $HMn(CO)_5$ catalyzed hydroformylation reaction [91]

600 psi CO/H_2 1:1, in toluene) and with all the organic substrates tested, the system proved to favor the production of linear aldehydes and some alcohols.

2.6 Bimetallic Systems

In homogeneous catalysis, also including hydroformylation reactions, the use of bimetallic or multimetallic complexes has been recognized as a relevant tool for organic synthesis. Indeed, the cooperative or successive interaction of two or more different metal centers with the substrate molecules can lead to enhanced catalytic acitivities and selectivities and, in some cases, to new reactions which cannot be achieved by using monometallic systems [93, 94]. The term commonly used to describe this combined application of more metals, leading to regio-, chemo-, and stereoselectivities not due to additive effects, is "synergism" [95]. A number of phenomena have been proposed to explain synergism in catalysis, such as cluster catalysis [96] and the catalytic binuclear elimination reaction (CBER) that is described in (1). The latter has been extensively investigated by Garland, demonstrating that CBER is present in hydroformylation reaction using rhodium–manganese and rhodium–rhenium mixed-metal systems.

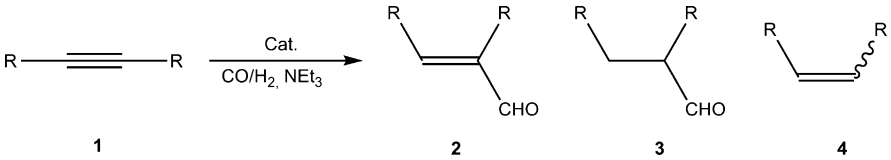
$$R^1M^1L_n + R^2M^2L_m \rightarrow R^1R^2 + M^1M^2L_{n+m} \quad (1)$$

The addition of manganese carbonyl hydride $Mn_2(CO)_{10}$/$HMn(CO)_5$ to rhodium precursor $Rh_4(CO)_{12}$ in the hydroformylation of 3,3-dimethylbut-1-ene led to a significant increase in system activity, yielding the aldehyde 4,4-dimethylpentanal in more than 95% selectivity [97]. Detailed in situ FT-IR spectroscopic measurements indicated that the increase in the rate of products formation was due to the existence of bimetallic catalytic binuclear elimination and, therefore, both mononuclear and dinuclear intermediates were present in the active system. Later studies on homogeneous catalyzed hydroformylation of cyclopentene to cyclopentanecarboxaldehyde, by using simultaneously rhodium carbonyl and manganese carbonyl complexes [98], confirmed previous observations. Kinetic data showed that the addition of manganese carbonyl hydride to rhodium catalyzed hydroformylation of cyclopentene increased the catalytic activity and promoted the precatalytic transformation of rhodium precursor to acyl-rhodium. In the hydroformylation of cyclopentene by using $Rh_4(CO)_{12}$ and $HRe(CO)_5$ as precursors, a very strong synergistic effect on the reaction rate was also observed [99]. As demonstrated earlier, mononuclear and binuclear intermediates were also detected in these bimetallic systems. The same observations on catalytic activities and mechanistic aspects were also encountered when these Rh–Mn and Rh–Re systems were applied for hydroformylation reaction of additional substrates [100].

The cluster complex $[Re_2Rh(\mu\text{-}PCy_2)(\mu\text{-}CO)_2(CO)_8]$ was found to be active in hydroformylation of 1-hexene under mild conditions (30 °C and 4 bar CO/H_2 1:1); in contrast, its dimanganese–rhodium analogue $[Mn_2Rh(\mu\text{-}PCy_2)(\mu\text{-}CO)_2(CO)_8]$ turned out to be much less active under the same conditions [101]. A series of dithiolato-bridged heterobimetallic MRh (M = Pt, Pd) were synthesized and tested as catalyst precursors in the hydroformylation of styrene. High pressure NMR experiments showed that only mononuclear species were formed under pressure conditions. Thus, in this case the catalytic activity could be attributed only to mononuclear rhodium species and no particular advantages could be obtained by using the heterobimetallic precursors [102]. No synergic effects were observed with the heterobimetallic $ZrRh_2$ complex $[Cp_2^{tt}Zr(\mu3\text{-}S)_2\{Rh(CO)_2\}_2]$ ($Cp^{tt} = \eta^5$-1,3-di-*tert*-butylcyclopentadienyl) [103] in the presence of P-donor ligands, but this catalyst precursor turned out to be a suitable catalyst in the hydroformylation of 1-octene under mild condition of temperature and pressure (80 °C, 7 bar CO/H_2 1:1).

The rhodium–molybdenum catalyst $[RhMo_6O_{18}(OH)_6]^{3-}$ supported in ordered mesoporous silica (FSM-16) was found to be more selective to produce butanols from propene hydroformylation than the monometallic precursor $RhCl_3$/FSM-16 (>98% vs 73%) [104]. Studies on the mechanism revealed that the formation of Mo–Rh alloy was crucial for selective synthesis of *n*-butanol. The addition of $Fe(CO)_5$ to [Rh(acac)(CO)L] (L = PPh_3, $P(OPh)_3$, $P(NC_4H_4)_3$) caused the increase of aldehydes yield in 1-hexene hydroformylation reaction up to 71%. Spectroscopic experiments (IR and NMR) proved the existence of an unstable bimetallic intermediate of the type $Rh(\mu\text{-}CO)_2Fe$, where rhodium and iron were bridged with two

Table 3 Hydroformylation of internal alkynes catalyzed by $PdCl_2(PCy_3)_2-Co_2(CO)_8$ or $PdCl_2(PCy_3)_2$ [80]



1 2 3 4

			GLC yield (%)		
R	Catalyst	Conversion (%)	**2**	**3**	**4**
^{n}Pr	$PdCl_2(PCy_3)_2-Co_2(CO)_8$	100	95	2	3
^{n}Bu	$PdCl_2(PCy_3)_2-Co_2(CO)_8$	97	90	2	5
^{n}Pen	$PdCl_2(PCy_3)_2-Co_2(CO)_8$	95	95	2	2
Ph	$PdCl_2(PCy_3)_2-Co_2(CO)_8$	99	53	0	30
Ph	$PdCl_2(PCy_3)_2$	94	77	0	15

For reaction conditions see [80]

carbonyl groups. This last probably facilitated dihydrogen activation and enhanced the stability of Rh−H bonding even at very low concentration of phosphorus ligands [105].

Bimetallic nanoparticles systems have recently attracted much attention for use as catalysts in hydroformylation reactions. Many examples of rhodium, cobalt, and palladium nanoparticles [36, 106] used in hydroformylations showed that reactivity increased with the nanoparticles compared to commercial grade and bulk metals. Heterobimetallic nanoparticles turned out to be superior compared to single nanometals, as in the case of Co_2Rh_2 [107]. In fact, when cobalt–rhodium nanoparticles on charcoal were used for hydroformylation of 1-dodecene under 30 atm CO/H_2 (1:1), a complete conversion and 76% of selectivity were achieved after 2 h reaction time. Under the same conditions, cobalt nanoparticles on charcoal (CNC) gave only a 22% conversion with a 48% of selectivity. In addition, when the reusability of Co_2Rh_2 was tested in recycling, there was no loss in conversion and selectivity after the fifth reaction cycle.

A synergic effect was also evident in ethylene hydroformylation carried out with the combination of $Ru_3(CO)_{12}$ and $Co_2(CO)_8$ on silica support [108]. The optimal atomic ratio of Co:Ru was assumed to be 3:1 and the derived system showed a satisfactory catalytic stability. The synergy between the two metals which led to the remarkable rate improvement in ethylene hydroformylation with respect to monometallic species was explained in terms of catalysis operated by bimetallic particles and by ruthenium and cobalt monometallic particles in intimate contact. As mentioned above, the bimetallic system $PdCl_2(PCy_3)_2-Co_2(CO)_8$ [80] was found to be effective in hydroformylation of various internal alkynes (Table 3). The combined system remarkably improved the catalytic activity especially the rate of the reaction, with little change of selectivity.

The Pd–Co/AC supported catalyst was encapsulated in a silicalite membrane and tested as catalyst in hydroformylation of 1-hexene with syngas. The catalytic performance of the encapsulated catalyst turned out to be enhanced with respect to Pd–Co/AC and the system also showed the advantage of improved selectivity of the linear products compared with branched products thanks to the spatial confined structures of the membrane [109]. In conclusion, Au nanoparticles deposited on Co_3O_4 led to remarkably high catalytic activities in hydroformylation reactions of different olefins [110]. Under mild conditions (100–140 °C, 3–5 MPa), the selectivity was above 85% to desired aldehydes and the Au/Co_3O_4 catalyst was recycled by simple decantation with slight decrease in catalytic activity along with an increase in recycle times, which is much more advantageous over homogeneous catalytic processes.

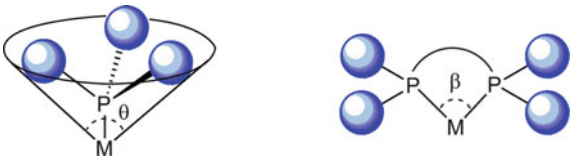
3 Controlling the Regio- and Enantioselectivities

3.1 General Considerations

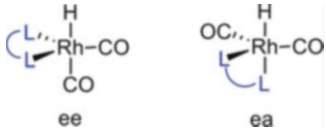
Much effort has long been focused on the development of efficient catalysts for hydroformylation of industrially relevant substrates such as linear olefins. Indeed, their respective aldehydes can be readily converted into secondary products such as alcohols, amines, carboxylic acids or esters that find application in the elaboration of many diverse products such as detergents, plasticizers and lubricants. There is now substantial research and commercial interest in making fine chemicals using this reaction. Thus, extension of the oxo process to more added-value olefins has gained increased interest over the past decade. This infatuation resulted especially from the need to access fine chemicals in a limited number of steps. Hydroformylation thus appeared as an atom-economic alternative to multi-step syntheses. Nonetheless, two primary challenges must be addressed for an effective and practical hydroformylation to be implemented; the control of regio- and enantioselectivities (so that only the desired isomer is formed) and the optimization of the catalyst system to allow substituted (sterically hindered) olefins to be functionalized under mild reaction conditions. Over the past decade, significant breakthroughs have been made in this direction through an accurate design of the ligands. New catalytic systems have emerged that are now suitable for linear or branched selective hydroformylation of terminal and internal alkenes and simultaneous control of both regio- and enantioselectivity.

Several parameters should be considered to determine how effective a ligand could be in the discriminating process leading preferentially to one isomer. First, the bulkiness of the coordinated ligand should be assessed using the Tolman angle for monodentate ligands and using the natural bite angle for bidentate ligands (Scheme 7).

Scheme 7 Tolman angle θ and natural bite angle β



Scheme 8 Bis-equatorial (ee) and equatorial–axial (ea) coordination modes of bidentate ligands (L–L) in the $[HRh(CO)_2(L–L)]$ complexes

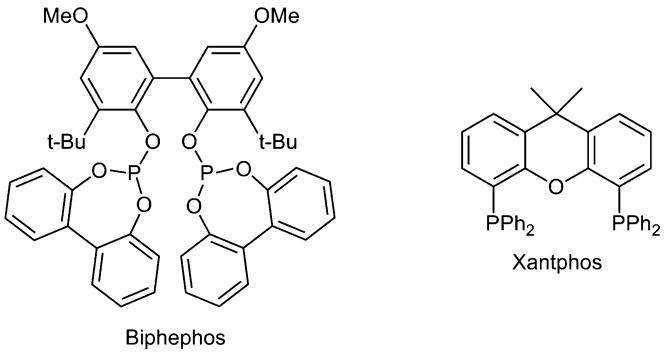


Second, for bidentate P-ligands, the rigidity of the spacer between the two-phosphorus atoms greatly affects their coordination ability. Third, depending on its bulkiness and rigidity, a ligand can coordinate the metal in an equatorial–equatorial (ee) or equatorial–axial (ea) coordination mode (Scheme 8). Eventually, electronic effects are also decisive to determine the regio- and enantioselective character of a ligand. In the following paragraphs, all these aspects are covered through a detailed study of the ligand structures and properties. Given the above conclusions on the metal properties (see Sect. 2), Rh-catalyzed hydroformylation has only been considered. Hydroformylation of benchmark olefins such as linear α-olefins, allyl cyanide, vinyl acetate, or styrene is not discussed in this chapter. This chemistry has been reviewed previously [111, 112] and for all details the reader is urged to consult these summaries, which allows this chapter to focus on the latest developments.

3.2 Linear Selective Hydroformylation

3.2.1 Bulkiness as a Paradigm

A long road has been covered and ample progress made since the utilization of PPh_3 as a metal-stabilizing ligand in hydroformylation. New phosphorus ligands have emerged with specific properties in terms of regioselectivity. Knowing that both alkenyl carbons can react during the hydroformylation process, ligands have been especially designed to orient the formyl group to the terminal position. As such, bulky P-ligands have especially attracted much attention as sterically encumbered ligands give rise to a reduced accessibility of the metal atom, thereby promoting the formation of linear aldehydes. Bidentate P-ligands appeared to be of particular interest. To assess the degree of congestion generated around the metal by the bidentate P-ligands, the concept of the "natural bite angle" was introduced in 1990 by Whiteker and Casey [113]. The natural bite angle is defined as the preferred angle created by two phosphorus atoms and a "dummy" metal atom (Scheme 7).



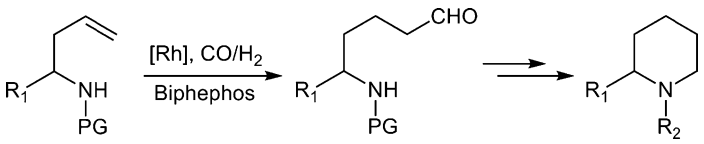
Scheme 9 Biphephos and xantphos ligands

The wider the natural bite angle the higher the steric hindrance. During the hydroformylation process, the formation of linear alkyl intermediates is generally explained by the steric hindrance between substituents at phosphorus and the alkenyl substrate [114, 115]. As shown by isotope and computational studies on xantphos catalysts, the repulsive interactions lead to preferential formation of the linear alkyl-rhodium intermediate when the P-donors occupy equatorial positions (Scheme 8). Generally speaking, bis-equatorial coordination of a bulky chelating P-ligand facilitates the linear selective hydroformylation [116, 117]. In addition to the steric effect, a large natural bite angle also induces an electronic effect as the structure of the intermediate Rh-species is significantly influenced by the kind of biphosphine used [118]. Thus, the bidentate P-ligand electronically favors or disfavors certain geometries of transition metal complexes. Below are detailed some of the main results obtained using bulky ligands in Rh-catalyzed linear selective hydroformylation.

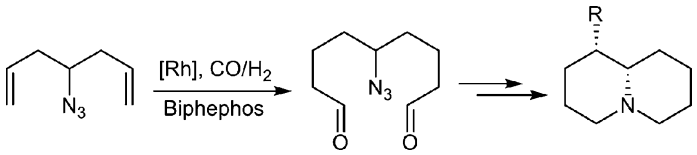
3.2.2 Hegemony of Biphephos and Xantphos Ligands

Most linear selective hydroformylations applied to fine chemicals have been achieved using biphephos and xantphos (Scheme 9). Biphephos is a bulky diphosphite ligand based on a bisphenol linker [119–121]. Xantphos, for its part, is built up from a xanthene backbone [117].

For years it has been a challenging task to develop catalysts for vinyl and allyl derivatives due to the chelating effect from the neighboring heteroatoms or arenes. Catalyst systems are now accessible that control the regioselectivity to make linear aldehydes in high yields. For example, the Rh/biphephos system was applied to the linear hydroformylation of allyl- and homoallylamines. The resulting oxo products were converted into different alkaloids encompassing the piperidine ring system, one of the most encountered cores in natural products and pharmaceuticals. For example, the linear selective hydroformylation of homoallylamines yields an aldehyde that collapses to an internal enamine that is easily convertible into two



Scheme 10 Linear selective hydroformylation of homoallylamines



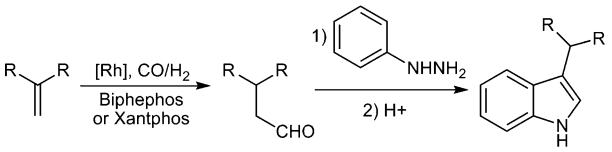
Scheme 11 Linear selective hydroformylation of an azido-containing dialkene

piperidine alkaloids, namely (±)-allo-sedamine and (±)-allo-lobeline (Scheme 10) [122]. In that case, the cyclohydrocarbonylation is a viable alternative to Ru-catalyzed metathesis for the transformation of homoallylamines to piperidines.

Hydroformylative cyclohydrocarbonylation (CHC) of homoallylamines in THF with the Rh(I)/biphephos catalytic system also leads to linear aldehydes which subsequently produced six-membered enamides in the presence of pyridinium *p*-toluenesulfonate [123]. The catalyst-based regiocontrolled assembly of different substituted heterocycles was possible without the need for functional group protection and with a reduced number of steps. The versatility of this strategy is demonstrated by syntheses of piperidines such as (±)-coniine, (±)-anabasine, (±)-dihydropinidine, and quinolizidines or (±)-alkaloid 9-epi-195C. The domino hydroformylation cyclization was extended to the synthesis of enantiomerically pure 2-, 2,3-, 2,6-, 2,3,6-substituted piperidines and 1,4-substituted indolizine [124]. Homoallylazides have also been used as direct precursors for the piperidine core [125]. Phosphites such as biphephos are more electronically deficient than phosphines, thus reacting very slowly with azides. The olefin conversion was good and the regioselectivity in favor of the linear aldehyde was >95%. Additionally, the azido function remained intact. Similarly, the total syntheses of two naturally occurring quinolizidine alkaloids, (+)-lupinine and (+)-epiquinamide, has been realized in eight and nine steps, respectively, using a bidirectional regioselective hydroformylation of chiral bishomoallylic azides as a key step (Scheme 11) [126].

Biphephos and xantphos have been used as sterically demanding bidentate ligands in a one-pot synthesis of tryptopholes and tryptamines via tandem hydroformylation/Fischer indole synthesis starting from allylic alcohols and allylic phthalimide (Scheme 12) [127].

Tryptamines are involved in various biological processes. Serotonin, for example, is a neurotransmitter and influences the human nervous system. Typically, without any ligand, low *l*/*b* ratios are obtained with allylic alcohols and amines if compared to normal terminal alkenes, due to intramolecular coordination of the hydroformylation catalyst to the allylic functionality. With biphephos as a ligand,

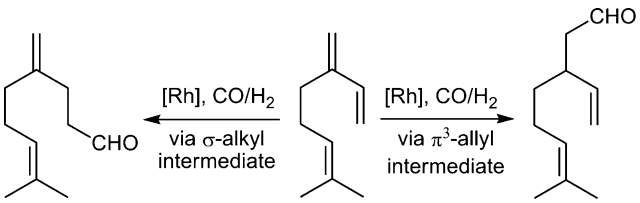


Scheme 12 Tandem hydroformylation/Fischer indole synthesis

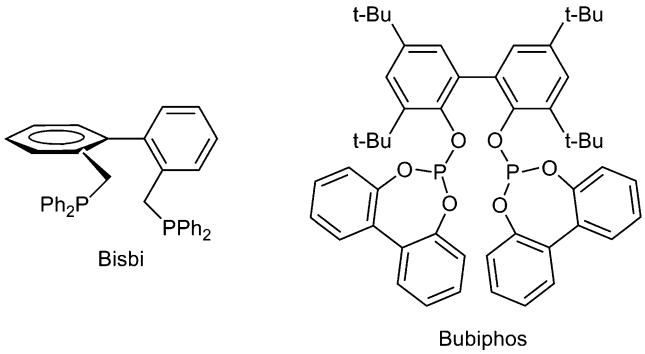
these allylic systems exclusively give the indoles derived from the linear products. If allylic phthalimide tryptamine is used, the product is obtained with only 26% yield and a poor *l*/*b* ratio of 2:1 because biphephos is less stable in the presence of aldehydes and undergoes acid-catalyzed decomposition. Use of the more stable xantphos (biphosphane ligand) leads to complete linear regioselectivity with increased yields of tryptamine (46%). Extension to pharmacologically relevant indoles has also been described [128]. Actually, in the presence of phenylhydrazine and the Rh/xantphos system, hydroformylation of *N*-allylic-*N*,*N*-dimethylamine and of 4-methylene-*N*-methyl piperidine leads to the expected aryl hydrazones in almost quantitative yields. The use of xantphos grants high linear selectivity in the hydroformylation of terminally monosubstituted amino olefins. No products stemming from branched aldehydes are detected. A protocol that allows direct access to tryptamine derivatives from amino olefins has also been developed in water. Solubility of the rhodium-based hydroformylation catalyst in water has been achieved by using the analogous derivative of xantphos. With allylic and homoallylic substrates containing the piperidyl or the piperazinyl moiety, high regioselectivities can be achieved with sulfonated xantphos in tandem hydroformylation/Fischer indole synthesis in water. Additionally, the two-component one-pot hydroformylation/Fischer indole synthesis sequence has been applied to 2,5-dihydropyrroles and phenyl hydrazines to access tetrahydro-β-carbolines [129]. Rh catalyst modified with diphosphine ligands such as dppf, Binap and dppb give no aldehyde at all or give low conversions of substrate. Xantphos yields a good regioselectivity but with a poor 37% yield. Phosphite ligand $P(OPh)_3$ and biphephos give good yields but had low influence on regioselectivity of the reaction.

Use of biphephos in hydroformylation of *N*-protected homoallylic amine resulted in complete selectivity for the linear isomer resulting in the formation of six-membered ring ene-carbamates [130]. Biphephos also proves to orient selectively the hydroformylation to the terminal position with unsaturated pyridyl derivatives [131]. 2-Substituted pyrrolidines are obtained with linear to branched ratio up to 5:1. From *N*-protected allylamines as starting materials and xantphos or biphephos as a ligand, a tandem hydroformylation/Wittig reaction allows for the regioselective synthesis of a β-proline precursor with linear to branched ratios up to 95:5 [132].

Through a detailed study on mono- and diphosphine ligands, Bayón et al. showed that both the ligand bite angle and flexibility could be incriminated to explain regioselectivity in the hydroformylation of myrcene [72]. Ligands with a bite angle near 120° and with a rigid backbone, such as xantphos, coordinate rhodium in equatorial–equatorial position and show preferential selectivities for



Scheme 13 Linear selective hydroformylation of myrcene



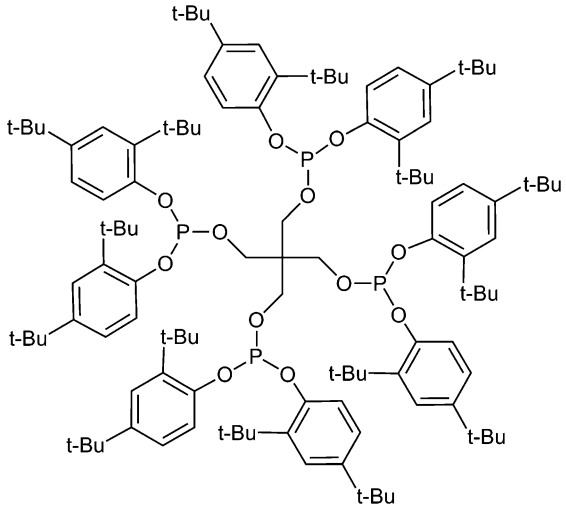
Scheme 14 Bisbi and bubiphos ligands

aldehydes originating from σ-alkyl intermediate (Scheme 13). However, the importance of the ligand rigidity was revealed by comparison with the more flexible bisbi and bubiphos (Scheme 14) that showed very low selectivity for aldehyde arising from linear σ-alkyl intermediate.

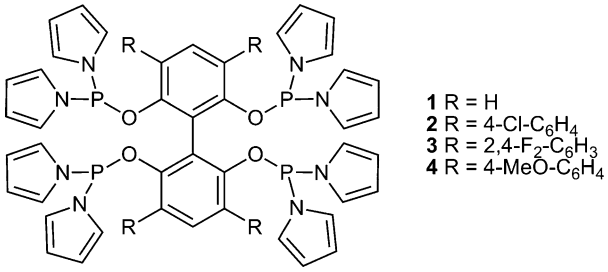
Thus, for ligands coordinating the metal in diequatorial positions in catalytically active species, a rigid backbone (such as xantphos) facilitates the formation of the σ-allyl intermediate while a flexible backbone (such as that of bisbi or bubiphos) favors η^3-allyl rhodium intermediate (Scheme 13). The opposite trend is observed for the ligands coordinating rhodium in axial–equatorial positions. Though coordinated in equatorial–equatorial position, completely flexible monodentate ligands such as PPh_3 (cone angle of 145°) yield mainly the products derived from the η^3-allyl intermediate in high selectivity, thus highlighting once again the need for a rigid ligand backbone for linear selective hydroformylation. The existence of a η^3-allyl rhodium intermediate determines the formation of an aldehyde at the terminal position because insertion of CO is slower than the isomerization process leading to the π-allyl complex.

3.2.3 Other Ligands

Other bulky ligands have also been elaborated to orient selectively the hydroformylation reaction at the terminal carbon. For example, 10 years ago [133],



Scheme 15 Tetraphosphite ligand (Mitsubishi Kasei Corp.)

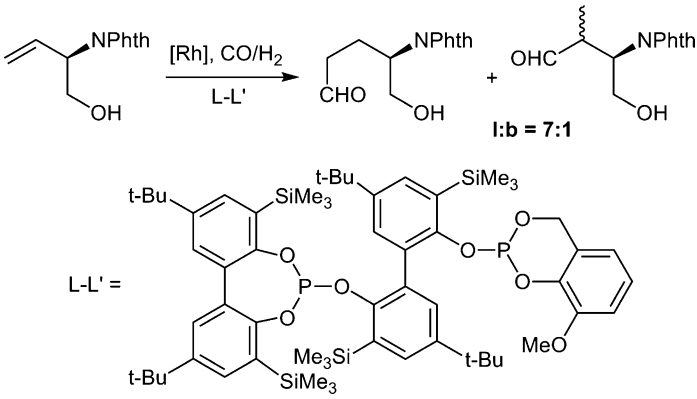


Scheme 16 Pyrrole-based tetraphosphorus ligand

cinchonidine, quinine, and quinidine could be hydroformylated with terminal selectivity up to 87% using a Rh-catalyst coordinated by a bulky polydentate phosphite ligand, a tetraphosphite developed by Mitsubishi Kasei (Scheme 15) [134]. Once hydroformylated, the naturally occurring cinchona alkaloids were then subjected to reduction reactions to create an extra functional group that allows immobilization.

Linear selective hydroformylation of functionalized vinyl and allyl derivatives is also of interest to access biologically active compounds such as γ-aminobutyric acid (GABA), 5-hydroxytryptamine (serotonin), or cinacalcet (a calcimimetic drug developed used for the treatment of hyperparathyroidism). As such, pyrrole-based tetraphosphorus ligands (Scheme 16) have proven to be effective to reverse the branch preference and afford linear aldehydes with high regioselectivities from allyl and vinyl derivatives bearing various functional groups [135].

In addition to considerations on the bite angle and the rigidity of the ligand backbone, this study showed that electronic effects are also of importance in



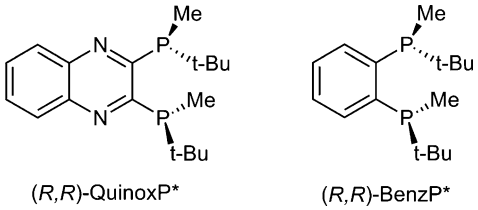
Scheme 17 Linear selective hydroformylation of (*R*)-*N*-phthalimido-vinylglycinol using a dissymmetric diphosphite ligand

controlling the regioselectivity towards linear aldehydes. Indeed, tetraphosphorus ligands that bear strong electron-withdrawing substituents such as 2,4-difluorophenyl groups at the 3,3′,5,5′-positions of the biphenyl backbone are the most effective. Conversely, methoxy substituents, which are strong electron-donating groups, afford the lowest linear selectivity. The attachment of a 4-methoxyphenyl group at the 3,3′,5,5′-positions of the biphenyl backbone do not result in a significant change in linear selectivity, indicating that there is little steric effect at the 3,3′,5,5′-positions on the hydroformylation regioselectivity. Hence, in addition to the ligand bulkiness around the metal, electronic effects are also of crucial importance for high linearities to be obtained.

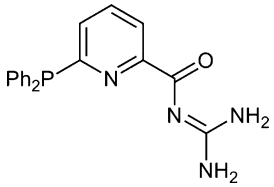
(*R*)-*N*-Phthalimido-vinylglycinol, owing to the three distinct functional groups in the four-carbon framework and the defined stereogenic center, has been used in the synthesis of a number of natural products and pharmacologically active agents [136]. The ligand described in Scheme 17 has proved especially effective for controlling the linear selective hydroformylation as a linear to branched ratio of 16:1 was obtained.

Recently, the P-chirogenic ligands (*R*,*R*)-QuinoxP* and (*R*,*R*)-BenzP* (Scheme 18) demonstrated remarkable stereochemical control in asymmetric hydroformylation of α-alkylacrylates affording the linear aldehydes in good to excellent yields (up to 91%) and high enantioselectivity (up to 94%) [137]. It is hypothesized that these structurally rigid P-chirogenic ligands are able to bring chiral information closer to the reaction site because (*R*,*R*)-QuinoxP* and (*R*,*R*)-BenzP* bear chiral information directly on phosphorus, rendering them uniquely effective in differentiating between the two olefin substituents. The resulting 2-isopropyl- and 2-cyclohexyl-1,4-dicarbonyl structures are particularly interesting in that they can be found in many biologically active compounds and active pharmaceutical ingredients such as Caspase 1 Inhibitor (Pfizer) and Matrix Metalloproteinase Inhibitor (Roche).

Scheme 18 P-chirogenic ligands (*R*,*R*)-QuinoxP* and (*R*,*R*)-BenzP*



Scheme 19 Pyridylacylguanidine-functionalized phosphine ligand



3.2.4 The Supramolecular Approach

Site-selective functionalization can also be directed by supramolecular interactions. A guanidine receptor unit for carboxylates and a triarylphosphine group as the donor for a transition metal (Scheme 19) have been combined to afford an effective ligand in the Rh-catalyzed hydroformylation of β,γ-unsaturated carboxylic acids [138]. The ligand acts as a temporary substrate-bound catalyst-directing group leading to high activities (TOF up to 250 h^{-1}) and regioselectivity (*l*/*b* ratio up to 23). The study has been successfully extended to a tandem hydroformylation–hydrogenation reaction of terminal and functionalized alkenes. Here again, the linear selective hydroformylation was favored using a phosphine ligand equipped with an acyl guanidine functionality [139].

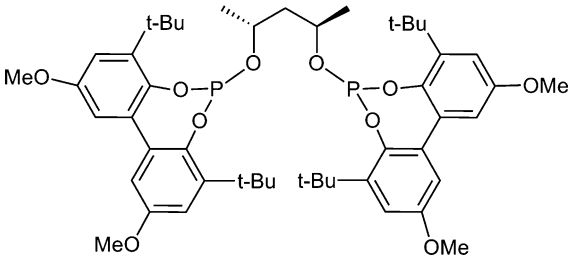
3.3 Branched Selective Hydroformylation

3.3.1 A Challenging Task

Branched selective hydroformylation offers great promise to the fine chemical industry. However, several technical challenges should be overcome before the reaction could be utilized on a commercial scale. Among them, controlling regio- and enantioselectivities concurrently is without doubt the most significant. The bisphosphite ligand (2*R*,4*R*)-chiraphite (Scheme 20) was the first effective ligand in Rh-catalyzed hydroformylation for the synthesis of anti-inflammatory 2-aryl-propionic acid drugs, such as (*S*)-naproxen [140, 141].

Since the discovery of chiraphite, many ligands have been synthesized aiming at extending the scope of substrates that can be hydroformylated in a regio- and enantioselective fashion to give fine chemicals. Through the numerous studies on ligand design and their catalytic performance, monodentate ligands generally lead

Scheme 20 (2*R*,4*R*)-Chiraphite (union carbide)



to very poor enantioselectivities, except the very bulky ones, highlighting the necessity of a multidentate ligand structure for optimum selectivity control. It also appears that the bulkiness and rigidity of the ligand are not as critical in this context as they can be for linear selective hydroformylation at least until the substrate is coordinated to the metal. Indeed, providing more access to the catalytic active site facilitates the approach of the olefin. However, once the substrate is coordinated at the branched position, high enantiomeric excesses generally result from a highly constrained environment. To perform this difficult task, two main approaches have been developed over the past decade. The first (Sect. 3.3.2) consisted in the elaboration of always more regio- and enantioselective ligands. The second (Sect. 3.3.3) deals with the utilization of catalytic amounts of P-ligands capable of binding the catalyst and the substrate at the same time, thus favoring contacts between them. Both strategies are detailed below.

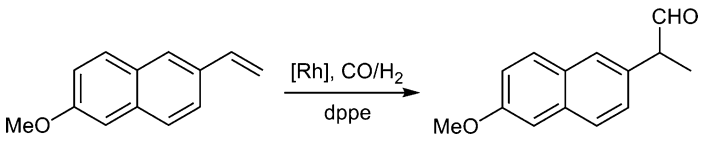
3.3.2 Phosphines, Phosphites, and Derivatives

Biphosphine Ligands

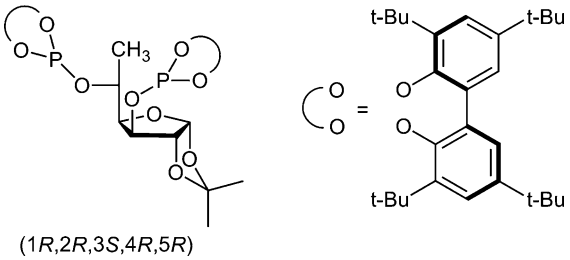
In contrast to linear selective hydroformylation, where bulky and rigid diphosphines are mainly used, branched selective hydroformylation required more adaptable ligands and/or ligands with low natural bite angle. In line with this assertion, the utilization of diphosphines as ligands to access branched aldehydes has been rarely described in the past 10 years for the synthesis of fine chemicals. Nevertheless, the chelating bidentate ligand (1,2-bis(diphenylphosphino)ethane, dppe) has proved to be effective in an alternative route for the synthesis of naproxen (Scheme 21) [142]. Because of the small bite angle of dppe (90°) and its equatorial–axial coordination mode (preferential formation of the η^3-allyl rhodium intermediate), 6-methoxy-2-vinylnaphthalene is easily converted into the branched (2-6-methoxynaphthyl) propanal (95%) using an Rh/dppe system. Subsequent oxidation of the oxo product gives D,L-naproxen.

Phosphite Ligands

Bisphosphites have been employed as ligands in branched selective hydroformylation for the synthesis of fine chemicals as they are more adaptable than



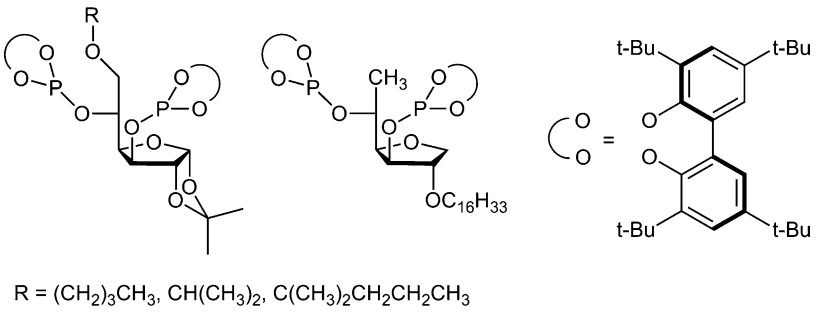
Scheme 21 Branched selective hydroformylation to D,L-naproxen precursor



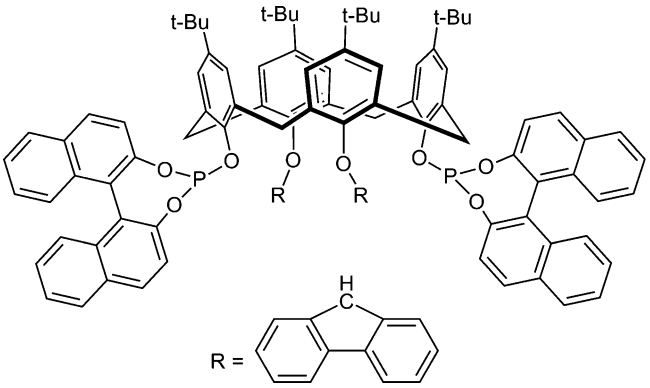
Scheme 22 Best sugar-based disphosphite ligands used in the Rh-catalyzed asymmetric hydroformylation of heterocyclic olefins

biphosphines around the catalytic site. Bisphosphites have greater conformational flexibility due to the intervening oxygen atoms. A comparative study has been performed on the catalytic performances of various glucofuranose-derived diphosphites whose phosphorus atoms have been substituted by biphenyl groups [143]. In the Rh-catalyzed asymmetric hydroformylation of 2,5-dihydrofuran, 1,3-diphosphites provided a better catalytic performance than 1,2- and 1,4-diphosphites, thus confirming that the flexibility of the spacer between the two phosphorus atoms should be carefully defined. It is worth pointing out that the bridge in the best sugar-based bisphosphite ligand represents a three-carbon linker between oxygen atoms similar to that found in (2*R*,4*R*)-chiraphite (Scheme 20). Additionally, bulky substituents in the *ortho* and *para* positions of the biphenyl moieties are needed for high enantioselectivity. The best ligand, a disubstituted furanoside 1,3-diphosphites (Scheme 22, R = CH_3), shows practically no isomerization with excellent regioselectivity (99%) and a relative high enantioselectivity (74% ee). Similar results are obtained in Rh-catalyzed asymmetric hydroformylation of 2,3-dihydrofuran and *N*-acetyl-3-pyrroline. The study has been extended to the hydroformylation of *cis*-4,7-dihydro-1,3-dioxepin and *cis*-2,2-dimethyl-4,7-dihydro-1,3-dioxepin. Here again, the presence of bulky substituents such as *tert*-butyldimethylsilyl groups on the biphenyl substituent greatly favors the enantioselectivity.

Other glucofuranose-derived 1,3-diphosphites (Scheme 23) have been applied to the Rh-catalyzed asymmetric hydroformylation of 2,5-dihydrofuran and 2,3-dihydrofuran [144]. A higher degree of isomerization is noted when increasing the steric hindrance at the C-6 position (and therefore at the Rh center). The β-H-elimination from Rh-alkyl intermediates is favored in that case. 2,3-Dihydrofuran is hydroformylated with excellent chemoselectivity (100%), good regioselectivity to aldehydes (up to 78%), and good enantioselectivity (up to 84%). The results are



Scheme 23 Glucofuranose-derived 1,3-diphosphites

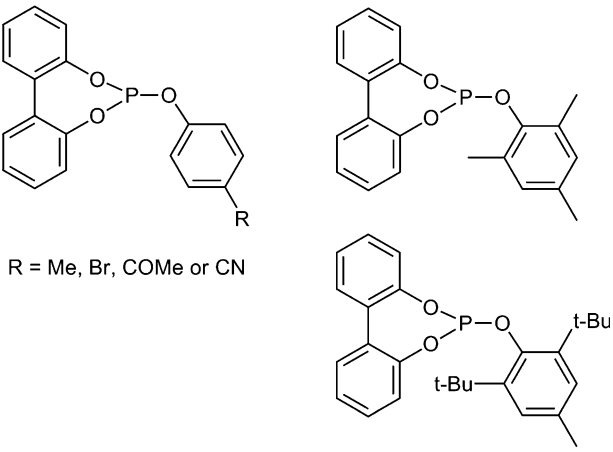


Scheme 24 Calix[4]arene-based diphosphite used in Rh-catalyzed asymmetric hydroformylation of norbornene

even better in hydroformylation of 2,5-dihydrofuran, especially using the $C_{16}H_{33}$-substituted ligand described in Scheme 23. Besides the excellent chemoselectivity (100%), the regioselectivity to aldehydes is total and the enantioselectivity reaches 88%.

A hemispherical diphosphite ligand with a conical calixarene skeleton (Scheme 24) can be used in the asymmetric Rh-hydroformylation of norbornene. Exclusive formation of the exo isomer is achieved with enantioselectivities up to 61% [145].

Interestingly, a series of monophosphite ligands based on the biphenol backbone has been reported in the Rh-catalyzed hydroformylation of enamides [146]. Enamides provide access to important amine derivatives, such as amino acids, amino alcohols, lactones, and β lactams, which show a wide range of biological properties. Exclusive formation of the branched aldehyde is observed for all the ligands described in Scheme 25. However, the results show a notable influence from the ligand electronic properties on the reaction rate. The more electron-withdrawing the substituent R, the faster the hydroformylation reaction. Logically, the electron-rich ligand having three methyl substituents attached give a slow



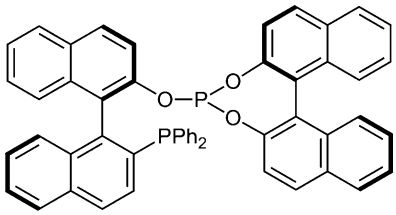
Scheme 25 Monophosphite ligands used in Rh-catalyzed hydroformylation of enamides

reaction rate. An electron-withdrawing group decreases the electron density of rhodium, which weakens the π back donation from the rhodium to CO, resulting in a faster CO dissociation. Interestingly, though very basic, the bulky *t*-Bu substituted ligand leads to the highest activity (TOF 350 h^{-1}). This is ascribed to the exclusive formation of monoligated Rh–phosphite complexes. Indeed, bulky ortho *t*-Bu groups prevent a bidentate coordination mode, thus decreasing the number of coordinated phosphites and making the rhodium electron-deficient. Similar results were reported by van Leeuwen and coworkers in the hydroformylation of substituted olefins such as 2,2-dialkylalkenes when using the bulky $P(O\text{-}o\text{-}tBuC_6H_4)_3$ as a ligand [147, 148].

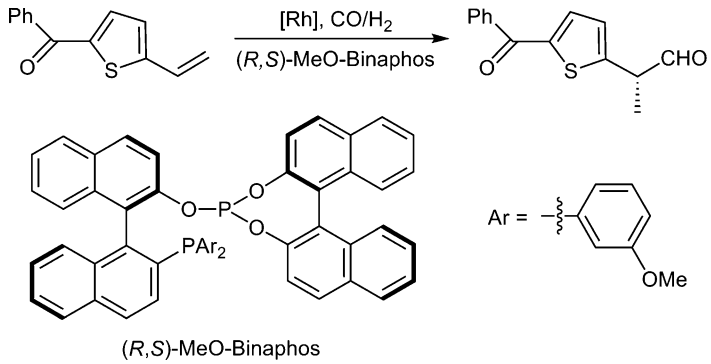
Phosphite–Phosphine Ligands

In the 1990s, phosphite–phosphine ligands have emerged as very powerful candidates for branched selective hydroformylation. For instance, ligands such as Binaphos (Scheme 26) [149] have shown their catalytic potential for many different substrates.

Over the past decade, the variety of substrates that could be hydroformylated using this ligand has been extended. For example, 2- and 3-vinylfurans could be regio- and enantioselectively hydroformylated [150]. A formyl group is selectively introduced at the α-position of the furan ring to give the isoaldehyde with a branched/linear ratio of 97:3 and 79% ee. Hydroformylation of 3-vinylfuran also gives the corresponding isoaldehyde with a regioselectivity of 90:10 in favor of the branched isomer and a high enantiomeric excess (>98%). The resulting aldehydes have a potential utilization as synthetic building blocks. For example, (2*R*)-2-(furan-2-yl)propanal could be a starting material to synthesize monensin and (2*S*)-2-(furan-2-yl)propan-1-ol, which should be obtained by reduction of the



Scheme 26 Binaphos ligand



Scheme 27 Branched selective hydroformylation to (*S*)-tiaprofenic acid precursor

asymmetric hydroformylation product of 2-vinylfuran, a key starting material for the 1,10-seco-eudesmanolide synthesis.

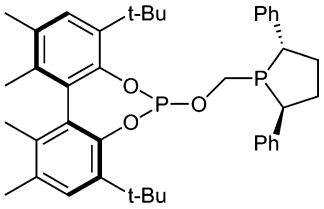
The asymmetric hydroformylation of vinyl heteroarenes (vinylfurans and vinylthiophenes) was investigated by using Rh(I)-(*R*,*S*)-MeO-BINAPHOS as a catalyst (Scheme 27) [151]. The hydroformylation of vinylthiophenes gave the corresponding branched aldehydes as major products with high enantiomeric excesses (up to 93% ee). Oxidation of the aldehydes successfully afforded α-heteroarylpropanoic acids which are an important class of compounds due to their biological activities. For example, tiaprofenic acid is known as one of the most popular nonsteroidal anti-inflammatory drugs.

Very recently, bobphos (Scheme 28), a hybrid non-*C*2 symmetric ligand derived from Kelliphite and Ph-bpe, has been found to give the branched aldehyde with significant selectivity in the hydroformylation of alkyl olefins of type $RCH_2CH{=}CH_2$ [152]. The corresponding branched aldehydes are of importance to the fragrance industry. Lillial, one of the most important of these fragrancies, was recently obtained from branched-selective hydroformylation with high enantioselectivity (92% ee).

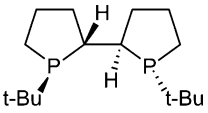
Bisphospholane Ligands

A major breakthrough in enantioselective hydroformylation was achieved with the syntheses of bisphospholane ligands. Until then, only Binaphos exhibited high

Scheme 28 (*S*,*S*,*S*)-Bobphos ligand



Scheme 29 (*S*,*S*,*R*,*R*)-Tangphos ligand



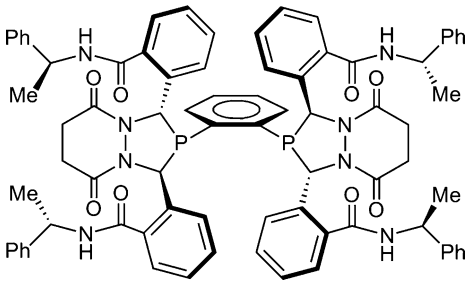
enantioselectivity for the asymmetric hydroformylation of both terminal and internal alkenes. However, poor regioselectivity and low catalyst activity limit the synthetic utility of this ligand. As described below, bisphospholane ligands allow for high chemo-, regio-, and enantioselectivities for a wide range of unsaturated substrates. Their performance mainly results from the small P–Rh–P bite angles [153]. Indeed, the structural and catalytic results suggest that the dihedral angle of the bridging biphenol in these bisphosphite ligands may play a role in controlling hydroformylation selectivity. Smaller dihedral angles are found to lead to increased regio- and enantioselectivity. Indeed, geometrical constraints force a decreased P–Rh–P bite angle when the bridging dihedral angle is decreased [154]. This is due to the conformational rigidity imposed by the direct connection of the phosphorus atoms to the biaryl. Generally speaking, the bite angles of bisphospholane ligands do not exceed 100°.

Highly enantioselective Rh-catalyzed hydroformylation of norbornene and derivatives mainly yields exo aldehydes with ees up to 92% using the diphospholane (*S*,*S*,*R*,*R*)-Tangphos (Scheme 29) [155]. Note that the results are much less convincing with the benchmark styrene for which harsher catalytic conditions are required and lower enantiomeric excesses are obtained (76% ee). More generally speaking, this study shows that the efficacy of a ligand should not only be determined using a single model substrate but that different families of substrates should be tested.

The Landis group has developed the synthesis of bisdiazaphospholane (BDP) ligands which display impressive activity with very high enantio- and regioselectivity for a variety of olefins [156]. Furthermore, such chiral aldehydes can be transformed immediately into diverse functional groups, increasing molecular complexity from a variety of readily available alkenes. For example, using (*S*,*S*,*S*)-BDP (Scheme 30), naproxen precursor 6-methoxy-2-vinyl naphthalene yields 96% ee and no detectable linear isomer [157]. Hydroformylation of *trans*-β-methylstyrene give the corresponding α-aldehyde, a precursor of antitussive butethamate, in 86% ee and 14:1 branched to linear ratio.

Rhodium complexes of (*S*,*S*,*S*)-BDP also catalyze the asymmetric hydroformylation of *N*-vinyl carboxamides, allyl ethers, and allyl carbamates with useful regioselectivity, high enantioselectivity (up to 99% ee), and complete conversion

Scheme 30 (*S*,*S*,*S*)-BDP ligand



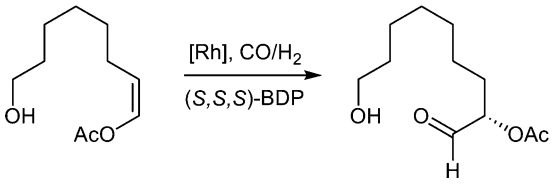
Scheme 31 Asymmetric hydroformylation as an alternate route to the Roche aldehyde

[158]. Substrates are successfully converted to chiral aldehydes within short reaction times (generally less than 6 h) and low catalyst loading (commonly 0.5 mol%). A prominent example is the Roche aldehyde, which is commonly prepared from the Roche ester (methyl 3-hydroxy-2-methylpropionate) in a three-step sequence. Asymmetric hydroformylation of allyl silyl ethers with (*S*,*S*,*S*)-BDP as the ligand proceeds with turnover frequencies >2,000 h^{-1} and turnover numbers exceeding 10,000 at 80 °C (Scheme 31). Chiral Roche aldehyde is obtained with 97% ee. Because of the low cost of allyl alcohol, a commodity chemical, and low catalyst loadings, asymmetric hydroformylation provides an attractive route to the Roche aldehyde. Commonly difficult substrates such as 1,1- and 1,2-disubstituted olefins also undergo effective hydroformylation using (*S*,*S*,*S*)-BDP as a ligand.

Hydroformylation of dienes presents many opportunities for the synthesis of both fine and commodity chemicals. In this context, regioselective and enantioselective Rh-catalyzed hydroformylation of 1,3-dienes has been efficiently performed using chiral BDP ligands, yielding β,γ-unsaturated aldehydes that retain a C═C functionality for further conversion [159]. Highly selective asymmetric hydroformylation extends to carboethoxy-1,3-pentadiene with the exclusive formation of the (*E*)-stereoisomer of the β,γ-unsaturated, 2-formyl aldehyde in 91% ee. In contrast to the synthetic route to the chiral aldehyde developed by Fürstner et al. in the total synthesis of Iejimalide B (six steps starting from enantiopure Roche ester) [160], the catalytic asymmetric hydroformylation of carboethoxy-1,3-pentadiene carried out with bisphospholanes ligands provides this aldehyde in one step.

Exhibiting both antifungal and antibacterial activities, the patulolides have been the targets of several total syntheses. Using (*S*,*S*,*S*)-BDP as a ligand, a highly atom-economical total synthesis of (+)-patulolide C has been accomplished in three steps from the known (2*R*)-8-nonyn-2-ol in 49% overall yield and 93% de [161]. A Rh-catalyzed asymmetric hydroformylation/intramolecular Wittig olefination cascade is utilized to set the C4-hydroxyl stereochemistry and *E*-olefin geometry as well as to form the macrolactone. Within 24 h 100% conversion to the C11-hydroxy-C4-acetoxyaldehyde (Scheme 32) is accomplished with complete regio-control and

Scheme 32 Asymmetric hydroformylation step in the total synthesis of (+)-patulolide C



Scheme 33 Asymmetric hydroformylation of vinyl OBO using (*R*,*R*,*S*)-BDP

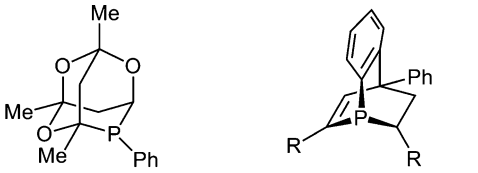
high diastereoselectivity. Only one aldehyde is observed as an equilibrium mixture with the hemiacetal. The asymmetric hydroformylation reaction yields a solution of aldehyde that is substantially pure, which can be utilized directly without purification.

Both enantiomers of Garner's aldehyde, a popular synthetic building block, are prepared from the same achiral alkene by catalytic asymmetric hydroformylation using (*S*,*S*,*S*)-BDP [162]. Rh-catalyzed asymmetric hydroformylation proceeds to afford the (*R*)-enantiomer with 13:1 regioselectivity in 94% ee and the (*S*)-enantiomer with 20:1 regioselectivity in 97% ee. Eventually, (*R*,*R*,*S*)-BDP ligands enable branched selective asymmetric hydroformylation of 1-vinyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane ortho ester (vinyl-OBO) with very low catalyst loading to afford the branched aldehyde with excellent regio- (branched to linear ratio of 12:1) and enantioselectivity (93% ee) (Scheme 33) [161]. Subsequent functionalization afforded (+)-Prelog-Djerassi lactone in a limited number of steps.

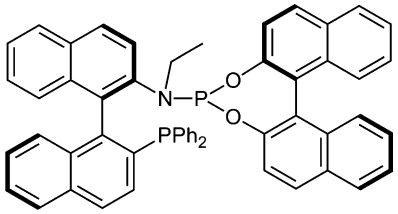
Other Ligands

Very few monodentate ligands have proved to be appropriate for branched selective hydroformylation. However, bulky structures showed very interesting catalytic properties. The use of the easily prepared, air-stable 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane (Scheme 34) enables hydroformylation of a range of 1,1-di- and 1,1,2-trisubstituted unsaturated esters [163]. Quaternary aldehydes are obtained with very good regioselectivities. For example, branched to linear ratios up to 50:1 are obtained in hydroformylation of methyl acrylate. More interestingly, hindered olefins such as methyl atropate or trisubstituted olefins are hydroformylated with branched to linear ratios up to 100:1. These results are of importance as they contradict the Keulemans rule that stated "addition of the formyl group to a tertiary C atom does not occur, so that no quaternary C atoms are formed" [164]. The influence of the cage monophosphine is dramatic, almost eliminating hydrogenation and retaining near-perfect regioselectivity. Subsequent reductive amination by imine hydrogenation of one of the quaternary aldehydes

Scheme 34 1,3,5,7-Tetramethyl-2,4,8-trioxa-6-phosphaadamantane (*left*) and phosphabarrelene ligands (*right*)



Scheme 35 (*R*,*S*)-Yanphos ligand

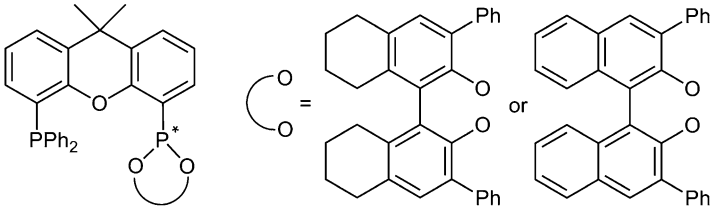


enables the synthesis of secondary amines, a common motif in compounds of pharmaceutical interest.

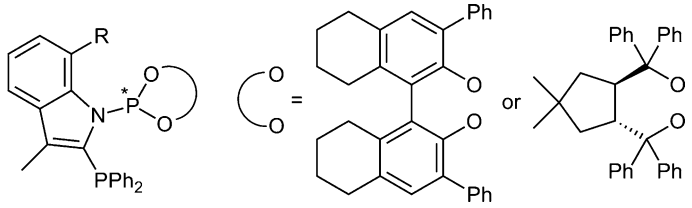
Phosphabarrelene–rhodium complexes (Scheme 34) display high activity in hydroformylation of poorly reactive internal alkenes. These systems allow for the hydroformylation of internal alkenes such as cyclohexene and cycloheptene with very high activity (TOF up to 12,231 h^{-1}) and simultaneous suppression of alkene isomerization. In hydroformylation of *N*-Boc-pyrroline, the Rh/2,4-xylylbarrelene operates isomerization free to give the 3-formyl-*N*-Boc-pyrroline under very mild reaction conditions as the exclusive product.

Apart from a few bulky monodentate ligands, non-classical bidentate ligands have also been used in branched selective hydroformylation to access fine chemicals. In this context, structure optimization of already well-known ligands has been achieved. For example, up to 98% ee is obtained for the hydroformylation of *p*-isobutyl styrene with (*R*,*S*)-Yanphos (Scheme 35), a phosphine–phosphoramidite ligand derived from Binaphos (Scheme 27) [165]. With Binaphos, only 92% ee is obtained. Oxidation of the aldehyde product affords the corresponding acid, ibuprofen, one of the most widely used nonsteroidal antiinflammatory agents. It has been shown that the enantioselectivity arises from the steric repulsion between the phenyl group of styrene and one of the naphthyl fragments of Yanphos [166].

Phosphine–phosphonite ligands built of a xantphos skeleton and a bulky substituent on the phosphorus atom (Scheme 36) have been utilized to hydroformylate dihydrofuran and pyrrolines, important precursors for the syntheses of versatile pharmaceuticals, natural products, and amino-acids [167]. In contrast with Binaphos, the two phosphorus nuclei of the xantphos-based ligands predominantly occupy bis-equatorial positions. High enantiomeric excesses (up to 91%) are obtained in the hydroformylation of 2,5-dihydrofuran along with excellent regioselectivities (>99.95%). Similarly, up to 91% ee and good regioselectivity (80:20) are obtained in the asymmetric hydroformylation of 2,3-dihydrofuran.



Scheme 36 Xantphos-based phosphine–phosphonites ligand



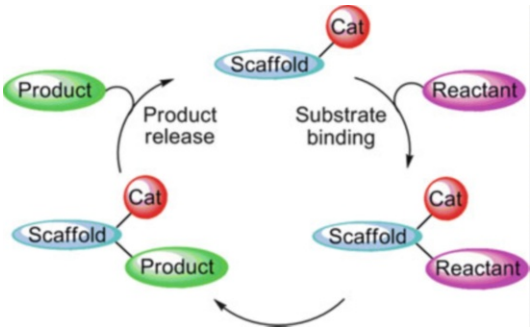
Scheme 37 Indole-based phosphine–phosphoramidites ligands

A comparison between the xantphos-based phosphine–phosphonite ligands and indole-based phosphine–phosphoramidite ligands (Scheme 37) enables one to assess the impact of the ligand bite-angle through the branched selective hydroformylation of dihydrofuran and pyrrolines [168]. Small bite angle indole-based phosphine–phosphoramidites ligands that coordinate exclusively in an equatorial–axial fashion in the catalytic resting state have been used in the highly selective asymmetric hydroformylation of the challenging substrate 2,3-dihydrofuran. The 2-carbaldehyde isomer was obtained as the major regioisomer in up to 68% yield and 62% ee. Conversely, the utilization of the large bite-angle xantphos-based phosphine–phosphonites that predominantly coordinate in an equatorial–equatorial mode completely changed the regioselectivity to the 3-carbaldehyde isomer with a high enantioselectivity of 91%. Of interest, 85% ee is obtained in the hydroformylation of *N*-acetyl-3-pyrroline with exceptionally high regioselectivities for the corresponding 3-carbaldehyde (>99%). The asymmetric hydroformylation of *N*-(*tert*-butoxycarbonyl)-3-pyrroline using the xantphos-based phosphine–phosphonites ligand yields the corresponding aldehyde (86% ee). Subsequent transformation of the aldehyde into the free carboxylic acid yields enantioenriched β-proline, a key structural element in peptides and proteins.

3.3.3 Directing Groups

Since the seminal works by Burke and Cobb in 1986 [169], the ligand-directing strategy has been widely exploited. In metal-based catalysis, ligands simultaneously act as reversible auxiliaries for the substrate and bind the metal, thus

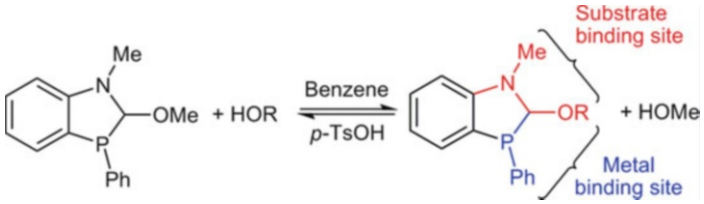
Scheme 38 Mechanism of the scaffolding ligand [170]



allowing for enhanced control of the selectivity of the transformation. Ideally, the ligand should have a useful functional group handle for future synthetic transformations. However, phosphorus-based ligands are the ideal ligands in hydroformylation and this functionality has limited application in organic synthesis. Accordingly, the P-ligand must be installed and removed from the molecule of interest, resulting in a stoichiometric byproduct. The strategy then appeared inherently inefficient. To avoid the use of stoichiometric amounts of directing groups, ligands have been used in a catalytic fashion. In 2008, the Tan group and the Breit group independently reported the concept of exchange reactions using a phosphorus-based ligand to allow for transient binding of substrate to a molecule that can direct the course of the reaction [170]. The reversibility of the bonding between the substrate and ligand allows branched selective hydroformylation to proceed using only a catalytic amount of ligand (Scheme 38). As such, the term "scaffolding ligands" has been used by analogy with scaffolding proteins, which promote various biological processes by bringing multiple proteins together. The term "catalytic catalyst-directing groups" was also coined for these phosphorus-based ligands.

The scaffolding ligand designed by Tan et al. consists of an alkoxy benzoazaphosphole ligand able to exchange rapidly with alcohols in the presence of catalytic amounts of *p*-TsOH [171]. Equilibration occurs with primary, secondary, and even tertiary alcohols at 45 °C (Scheme 39). The K_{eq} depends largely on the sterics of the alcohol, with isopropanol showing a tenfold decrease in binding to the ligand as compared to methanol, and *tert*-butanol exhibiting >100-fold change.

These ligands have both a substrate binding domain and a metal binding domain. The substrate binding domain allows for the reversible covalent binding of various organic functionalities while the metal binding domain facilitates the coordination of the metal catalyst. The entropic cost in binding together both the substrate and the metal catalyst allows for both acceleration of the reaction and control of regio- and stereochemistry. The concept has been applied to the conversion of many different substrates. The first example dealt with homoallylic alcohol substrates [171]. Whether it be terminal or disubstituted olefins, excellent diastereoselectivity (>98:2) and regioselectivity (up to 98:2) are obtained. In the same manner as for alcohols, protected amines such as sulfonamides can also bind to the scaffolding ligand and can be used in highly regioselective hydroformylation for synthesis of



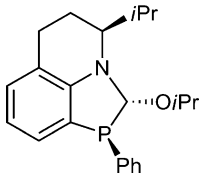
Scheme 39 Example of the scaffolding ligand [171]

β-amino-aldehydes [172]. The rate of exchange correlates with the acidity of the NH bond, with more acidic substrates exchanging faster. Regioselectivities up to 99:1 are observed in that case. The synthesis of β-amino-aldehydes has also been achieved through enantioselective hydroformylation of PMP-protected allylic amines [173]. The directed hydroformylation of disubstituted olefins occurs under mild conditions and (*Z*)-olefins afford excellent enantioselectivities (up to 93% ee). Aniline derivatives, another important class of molecules found broadly in biologically active compounds, have been subjected to catalytic scaffold-directed reactions [174]. A correlation between binding affinity and the yield and enantioselectivity of the hydroformylation reaction has been found. Substrates with high affinity for the ligand generally afford improved enantioselectivity. The benzoazaphosphole ligand (Scheme 39, R = *i*-Pr) has also been successfully applied to form quaternary stereocenters from substituted 1,1-disubstituted olefins that are particularly challenging in hydroformylation as a result of their low reactivity and high selectivity for the linear isomer. Excellent regioselectivity (up to 98:2) and high branch selectivity (up to 88:12) are obtained [175]. In all cases, regioselectivity levels were drastically degraded when PPh_3 was used as the ligand. An extension of the methodology to 1,2-di- and trisubstituted olefins as an alternative to the formaldehyde aldol process has also been described [176]. These reactions are performed under mild conditions and yield highly regioselective reactions. Hydroformylation of trisubstituted olefins allows the generation of two stereocenters in a stereospecific fashion.

The challenge of diastereoselectivity in hydroformylation has also been addressed using the concept of exchange reactions. As both the phosphorus and carbon stereocenters of the benzoazaphosphole ligand (O*i*Pr) undergo epimerization, a second-generation ligand was developed that incorporates a third non-epimerizable stereocenter, whose conformation is thermodynamically geared to have the adjacent phosphorus and carbon stereocenters anti, respectively [173]. As such, the chiral scaffolding ligand described in Scheme 40 was synthesized by introducing a tetrahydroisoquinoline group on the alkoxy benzoazaphosphole. Using this ligand, allylic anilines undergo efficient hydroformylation to afford chiral 1,3-amino alcohols with up to 93% ee.

The Breit research group demonstrated that Ph_2POMe was a suitable catalytic directing group for the highly branched-regioselective hydroformylation of homoallylic alcohols [177]. Phosphinites have been used as they are capable of reversible exchange with phenols and alcohols. In all cases the reactions proceed

Scheme 40 Chiral scaffolding ligand



smoothly with exceptional levels of regiocontrol to afford (after oxidation) the corresponding γ-lactones in good to excellent yields. Diphenylphosphinites also prove to be ideal systems for the reversible transesterification of bishomoallylic alcohols under hydroformylation conditions [178]. Hence, a highly regioselective hydroformylation can be realized using this catalyst system to furnish branched aldehydes selectively through a chelated transition state in an intramolecular manner. The system benefits from a short distance between the phosphorus atom and the olefin, allowing for excellent regioselectivities for both the homo- and bishomoallylic alcohols. The bishomoallylic alcohols undergo hydroformylation to form the six-membered ring heterocycles, in which excellent diastereocontrol for the anti product is observed when an allylic stereocenter is present. Eventually Ph_2POMe was successfully applied to the diastereoselective hydroformylation of cyclohexadienyl substrates with high stereocontrol [179]. The bicyclic lactones obtained are interesting building blocks with an attractive carbon quaternary center and additional alkene functions which can be subsequently functionalized. In this case, the directing group not only controls the selectivity of the reaction but also improves the overall efficiency of the transformation.

4 Conclusions and Perspectives

The advances that have been made during the past decade in Rh-catalyzed hydroformylation of olefins are impressive. A wider range of substrates can now be regio- and enantioselectively hydroformylated through judicious choice of the metal precursors and ligand. Throughout this chapter, it appears that the key to achieve high selectivities is not the type the phosphorus function involved in the coordination to the metal, but the particular spatial arrangement of the coordinated ligand. For example, subtle changes in the ligand bite angle can significantly influence the overall catalytic performance. While catalysts with a large P–Rh–P bite angle lead to increased formation of linear isomers, catalysts with a small P–Rh–P bite angle favor the formation of branched aldehydes.

Although the main metals known to be active as hydroformylation catalysts (Rh, Co) will probably continue to play a major role in the future, efforts have also been made to reach significant performances with other less expensive transition or non-transition metals, as demonstrated by some examples reported here.

This chapter is also a good illustration of the stimulating effect on innovative organometallic synthesis that can be achieved by exploration of scientific avenues that lie off the beaten track.

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Hydroformylation in Aqueous Biphasic Media Assisted by Molecular Receptors

Frédéric Hapiot, Hervé Bricout, Sébastien Tilloy, and Eric Monflier

Abstract The role of molecular receptors in aqueous biphasic hydroformylation of higher olefins is highlighted through a detailed analysis of their molecular recognition properties. The behavior of cyclodextrins and calixarenes as molecular receptors is especially emphasized and discussed. Their supramolecular interactions with the substrates and the water-soluble ligands proved to be an essential parameter guiding the reaction performances. The hydroformylation activity and chemo- and regio-selectivities can thus be accurately controlled by a suitable match between the receptor and the reaction components. Development outlooks are also presented.

Keywords Biphasic catalysis · Calixarenes · Cyclodextrins · Inclusion complexes · Molecular recognition

Contents

F. Hapiot, H. Bricout, S. Tilloy, and E. Monflier (✉)
Eric Monflier, Université d'Artois, Unité de Catalyse et de Chimie du Solide, CNRS UMR 8181, Faculté des Sciences Jean Perrin, SP18, 62307 Lens Cedex, France
e-mail: eric.monflier@univ-artois.fr

Abbreviations

3-α-1	2,3-Dimethyl-6-(3-sulfonato-*n*-propyl)-α-cyclodextrin potassium salt
3-β-1	2,3-Dimethyl-6-(3-sulfonato-*n*-propyl)-β-cyclodextrin potassium salt
4-α-1	2,3-Dimethyl-6-(3-sulfonato-*n*-butyl)-α-cyclodextrin potassium salt
4-β-1	2,3-Dimethyl-6-(3-sulfonato-*n*-butyl)-β-cyclodextrin potassium salt
4-β-2	2,3-Diethyl-6-(3-sulfonato-*n*-propyl)-β-cyclodextrin potassium salt
acac	Acetylacetonate
AC-β-CD	2,6-Diacetyl-β-cyclodextrin
BiphTS	Tris(*p*-sulfonatobiphenyl)phosphine trisodium salt
CRYSME-β-CD	Randomly methylated-β-cyclodextrin (substitution degree = 5)
DIME-α-CD	2,6-Dimethyl-α-cyclodextrin
DIME-β-CD	2,6-Dimethyl-β-cyclodextrin
h	Hour(s)
HP-α-CD	Hydroxypropyl-α-cyclodextrin
HP-β-CD	Hydroxypropyl-β-cyclodextrin
HTMAP-α-CD	*O*-(2-Hydroxy-3-trimethylammonio-*n*-propyl)-α-cyclodextrin chloride
HTMAP-β-CD	*O*-(2-Hydroxy-3-trimethylammonio-*n*-propyl)-β-cyclodextrin chloride
L	Liter(s)
Me	Methyl
min	Minute(s)
mol	Mole(s)
MTMAP/ME-α-CD	*O*-(2-Methoxy-3-trimethylammonio-*n*-propyl)-α-cyclodextrin
Ph	Phenyl
polyNAS	Poly(*N*-acryloyloxysuccinimide)
RAME-α-CD	Randomly methylated α-cyclodextrin (substitution degree = 10.8)
RAME-β-CD	Randomly methylated-β-cyclodextrin (substitution degree = 12.6)
RASBE/ME-β-CD	Randomly methylsulfobutylether-β-cyclodextrin
RASBE-β-CD	Randomly sulfobutylated-β-CD
SBE-β-CD	Sulfobutylether-β-cyclodextrin
SULFA-β-CD	Sulfated-β-cyclodextrin
t-Bu	*tert*-Butyl
TPPMS	*m*-Monosulfonatophenyldiphenylphosphine sodium salt

TPPTS	Tris(*m*-sulfonatophenyl)phosphine trisodium salt
TRIME-β-CD	2,3,6-Trimethyl-β-cyclodextrin
α-CD	α-Cyclodextrin
α-D-GluP	α-D-Glucopyranose
β-CD	β-Cyclodextrin
γ-CD	γ-Cyclodextrin

1 Introduction

In 1998 Anastas and Warner defined the 12 principle of "green" chemistry to aid one in assessing how green a chemical, a reaction, or a process is [1]. Among these principles, reusability and catalysis are of great importance with potential outcomes in reducing toxicity, pollution, and waste and improving energy efficiency and resource use. As such, metal-catalyzed hydroformylation in an aqueous/organic two-phase system appears to be an economical and safe approach for the production of linear and/or branched aldehydes (Fig. 1) [2].

In this biphasic process, the catalyst can simply be recovered by phase separation, thus decreasing the production costs and environmental impact. Unfortunately, the industrial viability of the biphasic hydroformylation process is limited to lower olefins such as propene and butene with an Rh/TPPTS (TPPTS = tris(*m*-sulfonatophenyl)phosphine trisodium salt) catalytic system (Fig. 2) [3–6].

The water solubility of higher olefins (five or more carbon atoms) is too low for very good rates to be achieved. Yet their hydroformylation products could lead to major industrial compounds such as detergent alcohols, plasticizers, and other chemicals. In order to circumvent this crucial problem, the utilization of co-solvent [7, 8], surfactants [9–17], amphiphilic phosphines [18–21], polymers [22], dispersed particles [23], and molecular receptors [24] has been reported. This chapter deals in particular with molecular receptors (especially cyclodextrins (CDs) and calix[*n*]arenes) as mass transfer promoters in aqueous organometallic catalysis and reflects both the understanding of the receptor-based catalytic systems and the intensity of the research activities focused on them. The chapter is divided into two main parts. CDs are discussed first, followed by calixarenes. For each supramolecular host, references to recent key papers are given to provide an entry to the literature.

2 Cyclodextrins as Molecular Receptors

Several topics are addressed throughout the following paragraphs. After a brief description of CDs, we report their utilization in combination with a TPPTS-based catalytic system. The interactions between CDs and the water soluble catalysts are

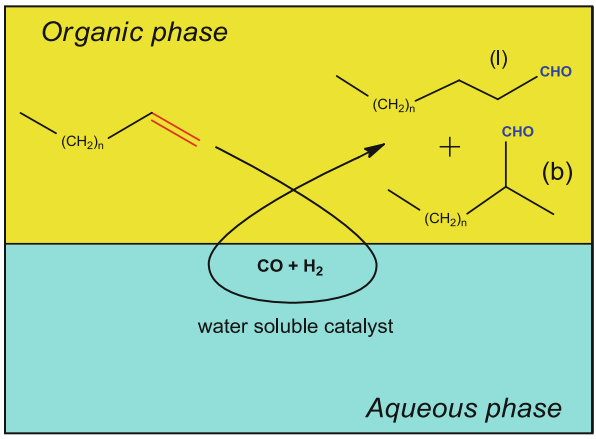
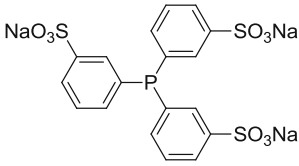


Fig. 1 Aqueous biphasic metal-catalyzed hydroformylation of alkenes



TPPTS

Fig. 2 Water-soluble TPPTS ligand used for aqueous biphasic hydroformylation

then discussed to explain the effect of chemically modified CDs on catalytic performance. Finally, the utilization of other CD/water-soluble ligands couples is also reported.

2.1 Cyclodextrins: A Short Description

Cyclodextrins are a class of naturally occurring receptors which are cyclic oligosaccharides constituted of six (α-CD), seven (β-CD), or eight (γ-CD) D-glucopyranose units (Fig. 3) [25]. Their shape is a conical cylinder whose wider opening is surrounded by all secondary hydroxyl groups while the narrower opening contains all the primary ones. The inner surface is hydrophobic and the outer surface hydrophilic. Their strong binding affinity for guest molecules makes them suitable for applications in analytical chemistry, agriculture, the pharmaceutical industry, and foodstuffs, toilet articles, and textile processing [26]. The utilization of native CDs as mass transfer promoters in aqueous organometallic catalysis has also been demonstrated [27], especially for the deoxygenation of allylic alcohols [28], oxidation of olefins [29–31], reduction of α,β-unsaturated acids [32], α-keto esters [33], or conjugated dienes [34]. They could also be used in the reduction of aryl alkyl ketones and aromatic aldehydes to hydrocarbons catalyzed by a dimer of chloro

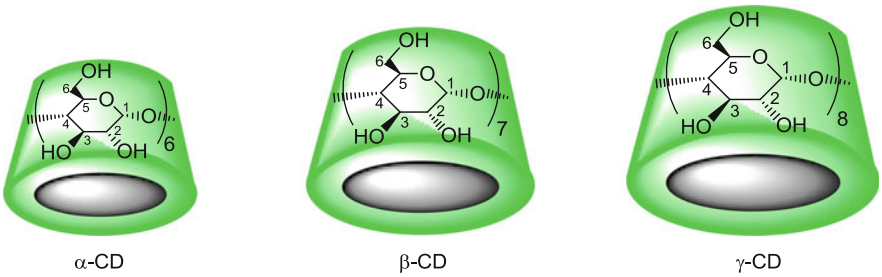


Fig. 3 Native α-, β-, and γ-CDs

(1,5-hexadiene)rhodium(I) [35]. The reaction rate strongly depends on the nature of the CD as the native β-CD promoted the reaction while the yields in the presence of native α-CD were lower than those observed without CD. Adverse effects of native CDs on transition metal catalyzed reactions have also been reported in two other reactions. Thus, addition of α-CD and β-CD inhibited the aldehyde reduction using the ruthenium complex $[RuCl_2(TPPMS)_2]$ (TPPMS: monosulfonated triphenylphosphine) [36] and the 1-hexene hydroformylation using rhodium catalyst $[RhH(CO)(TPPMS)_3]$ [37], respectively. The detrimental effect of the CD was attributed to interactions between the CD and the catalyst although no spectroscopic evidence could be obtained.

2.2 CD/TPPTS Combination

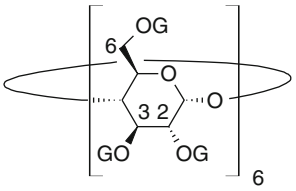
2.2.1 Effect of Modified Cyclodextrins upon Catalytic Activity

During the past 15 years we developed the use of chemically modified CDs as mass transfer promoters in aqueous organometallic catalysis [38–44]. In particular, we showed that modified CDs allowed us to achieve hydroformylation of higher olefins with high reaction rate and chemo- and regioselectivities, while avoiding the formation of an emulsion and the partition of the rhodium catalyst between the organic and aqueous phases [24]. The formation of inclusion complexes between hydrophobic olefins and chemically modified CDs was considered to be the key parameter of CD-based hydroformylation processes. All the CDs tested in the aqueous hydroformylation reaction are gathered in Tables 1 and 2.

The efficiency of the CDs has been assessed through consideration on the initial reaction rate. The results obtained in the rhodium-catalyzed hydroformylation of various α-olefins (1-octene, 1-decene, and 1-dodecene) at 80°C under 50 atm CO/H_2 (1/1 mixture) are gathered in Table 3.

Among the range of CDs, the randomly methylated β-CD (RAME-β-CD) appeared as a very promising candidate to develop an industrial process as it is non-toxic, cheap, biodegradable, and industrially available in large quantities. As

Table 1 Structure of α-cyclodextrin derivatives used in biphasic rhodium catalyzed hydroformylation



Abbreviation	Substituent (R)	Carbon bearing the OR group	Number of R group by CD	Source
α-CD	(–)	(–)	0	com. av.[a]
HP-α-CD	$-CH_2C(OH)CH_3$	2, 3 and 6	3.6	com. av.[a]
DIME-α-CD	$-CH_3$	2 and 6	10.8	[45]
RAME-α-CD	$-CH_3$	2, 3 and 6	10.8	[46]
HTMAP-α-CD	$-CH_2CH(OH)CH_2\overset{+}{N}(CH_3)_3\overset{-}{Cl}$	2	1	[47]
MTMAP/ME-α-CD	$-CH_2CH(COCH_3)CH_2\overset{+}{N}(CH_2)_3\overset{-}{Cl}$	2	1	[48]
	and $-CH_3$	2, 3 and 6	13	
3-α-1	$-(CH_2)_3-SO_3K$	6	6	[49]
	and $-CH_3$	2 and 3	12	
4-α-1	$-(CH_2)_4-SO_3K$	6	6	[49]
	and $-CH_3$	2 and 3	12	

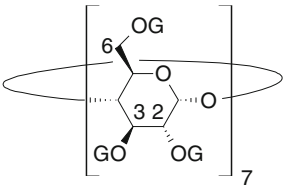
[a]This cyclodextrin is commercially available from chemical reagent suppliers or companies such as Sigma/Aldrich, Across, Cyclolab, Wacker-Chemie, or Roquette Frères

shown in Fig. 4, the reusability of the Rh/TPPTS/RAME-β-CD catalytic system has been demonstrated as five consecutive catalytic cycles have been performed without loss of activity in Rh-catalyzed hydroformylation of 1-decene [51]. Moreover, the phase separation between the organic and aqueous phases was fast and the rhodium and phosphorus contents in the organic phase were found to be less than 0.5 and 1.2 ppm respectively [52].

Note that the ability of RAME-β-CD to increase the reaction rate without impeding an efficient catalyst recovery was also confirmed by Kalck et al. in the hydroformylation of 1-octene or 1-decene using the $[Rh_2(\mu\text{-}StBu)_2(CO)_2(TPPTS)_2]$ bimetallic rhodium species [53].

The impact of the RAME-β-CD concentration on the biphasic system activity has been investigated by measuring the turnover frequency (TOF) as a function of the RAME-β-CD/Rh ratios [54]. The TOF linearly increases up to a ratio of 30, suggesting that the overall rate of the reaction is under mass transfer control.

Table 2 Structure of β-cyclodextrin derivatives used in biphasic rhodium catalyzed hydroformylation



Abbreviation	Substituent (R)	Carbon bearing the OR group	Number of R group by CD	Source
β-CD	(–)	(–)	0	com. av.[a]
CRYSME-β-CD	$-CH_3$	2, 3, and 6	5	com. av.[b]
RAME-β-CD	$-CH_3$	2, 3, and 6	12.6	com. av.[a]
DIME-β-CD	$-CH_3$	2 and 6	14	com. av.[a]
TRIME-β-CD	$-CH_3$	2, 3, and 6	21	com. av.[a]
AC-β-CD	$-COCH_3$	2, 3, and 6	14	com. av.[a]
HP-β-CD	$-CH_2-CHOH-CH_3$	2, 3, and 6	4.2	com. av.[a]
HP-β-CD	$-CH_2-CHOH-CH_3$	2, 3, and 6	5.6	com. av.[a]
HTMAP-β-CD	$-CH_2CH(OH)CH_2\overset{+}{N}(CH_2)_3Cl^-$	2	1	[47]
SULFA-β-CD	$-SO_3Na$	2, 3, and 6	9	com. av.[a]
SBE-β-CD	$-(CH_2)_4-SO_3Na$	2	1	[44]
RASBE-β-CD	$-(CH_2)_3-SO_3Na$	2, 3, and 6	7	[44]
RASBE/ME-β-CD[c]	$-(CH_2)_3-SO_3Na$ and $-CH_3$	2, 3 and 6	11 5	[50]
3-β-1	$-(CH_2)_3-SO_3K$ and $-CH_3$	6 2 and 3	7 14	[49]
4-β-1	$-(CH_2)_4-SO_3K$ and $-CH_3$	6 2 and 3	7 14	[49]
4-β-2	$-(CH_2)_3-SO_3Na$ and $-CH_2-CH_3$	6 2 and 3	7 14	[50]

[a]This cyclodextrin is commercially available from chemical reagent suppliers or companies such as Sigma/Aldrich, Across, Cyclolab, Wacker-Chemie, or Roquette Frères
[b]This cyclodextrin is commercialised by Roquette Frères (Lestrem, France) under the name KLEPTOSE® CRYSMEB
[c]RASBE/ME-β-CD was a randomly sulfobutylated CRYSME-β-CD

At higher RAME-β-CD/Rh ratio, a change in the slope of the curve indicates a change of the limiting step. TOFs have also been measured as a function of the temperature in a range from 40 to 120°C. The activation parameters were then calculated from a classical Arrhenius plot and confirmed that mass transfer is the kinetically limiting step (Fig. 5). Over 60°C ($1/T = 3.00\ K^{-1}$), the activation

Table 3 Relative reaction rate, aldehydes selectivity and linear to branched aldehyde (*l*/*b*) ratio for rhodium-catalyzed hydroformylation of higher olefins[a]

Entry	Olefin	CD	Relative reaction rate[b]	Aldehydes selectivity (%)[c]	*l*/*b*[d]
1[e]	C_8H_{16}	(–)	1	33	2.8
2	C_8H_{16}	RAME-α-CD	190	99	3.0
3	C_8H_{16}	HP-α-CD	55	98	2.9
4	C_8H_{16}	RAME-β-CD	175	97	1.7
5[f]	$C_{10}H_{20}$	(–)	1	59	2.8
6	$C_{10}H_{20}$	α-CD	12	85	3.2
7	$C_{10}H_{20}$	DIME-α-CD	42	94	2.8
8	$C_{10}H_{20}$	RAME-α-CD	84	91	3.0
9	$C_{10}H_{20}$	HP-α-CD	48	88	3.0
10	$C_{10}H_{20}$	HTMAP-α-CD	28	93	3.6
11	$C_{10}H_{20}$	MTMAP/ME-α-CD	100	98	3.1
12	$C_{10}H_{20}$	3-α-1	117	58	2.5
13	$C_{10}H_{20}$	4-α-1	128	54	2.6
14	$C_{10}H_{20}$	β-CD	24	80	2.1
15	$C_{10}H_{20}$	CRYSME-β-CD	66	96	1.8
16	$C_{10}H_{20}$	RAME-β-CD	192	98	1.7
17	$C_{10}H_{20}$	TRIME-β-CD[g]	36[g]	57[g]	2.5[g]
18	$C_{10}H_{20}$	HP-β-CD (4.2)[h]	96	82	1.9
19	$C_{10}H_{20}$	HP-β-CD (5.6)[h]	62	84	2.0
20	$C_{10}H_{20}$	AC-β-CD	110	57	2.6
21	$C_{10}H_{20}$	HTMAP-β-CD	30	94	1.9
22	$C_{10}H_{20}$	SULFA-β-CD	0.5	69	2.8
23	$C_{10}H_{20}$	SBE-β-CD	21	59	2.4
24	$C_{10}H_{20}$	RASBE-β-CD	60	57	2.1
25	$C_{10}H_{20}$	RASBE/ME-β-CD	160	58	2.6
26	$C_{10}H_{20}$	3-β-1	210	60	2.6
27	$C_{10}H_{20}$	4-β-1	250	62	2.5
28	$C_{10}H_{20}$	4-β-2	272	64	2.3
29[i]	$C_{12}H_{24}$	(–)	1	67	2.8
30	$C_{12}H_{24}$	HP-α-CD	12	84	2.9
31	$C_{12}H_{24}$	RAME-α-CD	25	92	2.8
32	$C_{12}H_{24}$	RAME-β-CD	120	90	1.9

[a]Experimental conditions: $Rh(acac)(CO)_2$: 0.04 mmol, TPPTS: 0.21 mmol, CD: 0.48 mmol, water: 11.5 mL, olefin: 20.35 mmol, *n*-undecane (internal standard): 2.03 mmol, $P(CO/H_2$: 1/1) = 50 bar, $T = 80°C$

[b]The relative reaction rate is the ratio between the initial catalytic activity measured with CD to that measured without CD

[c]Aldehydes selectivity = (mol. of aldehydes)/(mol. of converted olefins) × 100. The side products are mainly isomeric olefins

[d]Linear to branched aldehydes ratio

[e]The reaction rate for 1-octene hydroformylation without CD is 112 μmol/h

[f]The reaction rate for 1-decene hydroformylation without CD is 93 μmol/h

[g]The TRIME-β-CD was partially soluble in the reaction medium

[h]The average number of hydroxypropyl groups per CD is indicated between brackets

[i]The reaction rate for 1-dodecene hydroformylation without CD is 72 μmol/h

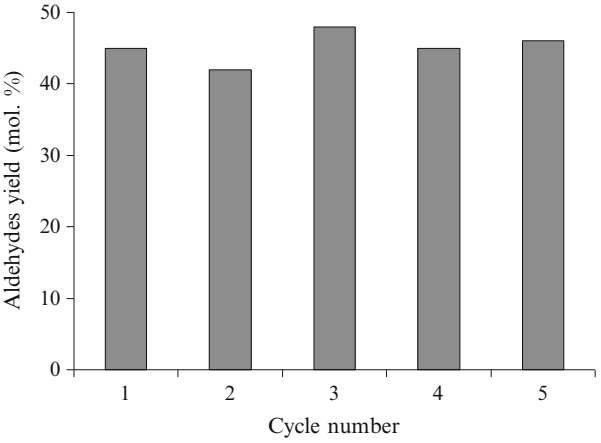


Fig. 4 Reusability of the Rh/TPPTS/RAME-β-CD catalytic system in biphasic 1-decene hydroformylation. Experimental conditions: $Rh(acac)(CO)_2$, 0.16 mmol, TPPTS: 0.8 mmol, RAME-β-CD: 1.12 mmol, water: 45 mL, 1-decene: 80 mmol, *T*: 80°C, $P(CO/H_2)$: 50 bar, reaction time: 1 h

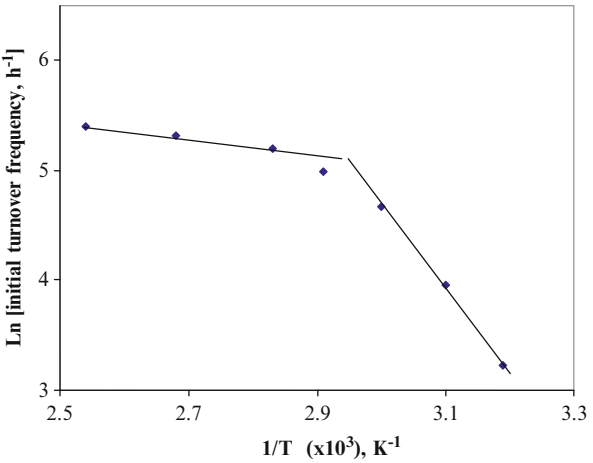


Fig. 5 Initial rate dependence on the reaction temperature. Experimental conditions: $Rh(acac)(CO)_2$: 0.04 mmol, TPPTS: 0.021 mmol, RAME-β-CD: 0.48 mmol, water: 11.5 mL, 1-decene: 20.5 mmol, $P(CO/H_2)$: 50 bar

energy value (5.8 kJ mol^{-1}) was characteristic of a process dependent on the diffusion of reactants and products between the aqueous and organic phases and was not related to the reactivity of the catalytic organometallic species.

Interestingly, a synergetic effect between randomly methylated α- and β-CDs has been evidenced in Rh-catalyzed hydroformylation of 1-tetradecene [55]. Indeed, a marked positive nonlinear effect on 1-tetradecene conversion was observed when the CD molar ratio in the mixture was modified. The explanation probably lies in the formation of 2:1 ternary inclusion complexes between RAME-CDs and the olefin.

Finally, a Co/TPPTS combination was also studied in the presence of CDs [56]. Good conversion (>92%) and selectivity (>92%) could be obtained in Co-catalyzed hydroformylation of higher olefins without impeding the recovery of the catalytic system. The Co/TPPTS/RAME-β-CD catalytic system was

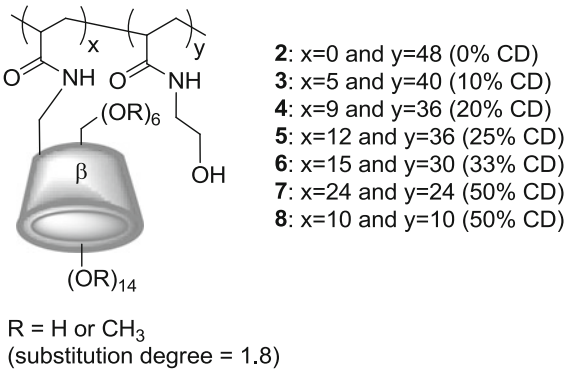


Fig. 6 β-CD-functionalized polymers 2–8

successfully recycled four times. Furthermore, the phase separation was fast and no emulsion was observed at the end of the reaction.

2.2.2 Cyclodextrin-Based Polymers for Long Alkyl Chain Olefins

The mass transfer limitation between the aqueous and organic phases could also be overcome using CD-based polymers, especially for the Rh-catalyzed hydroformylation of long-alkyl chain olefins. Indeed, catalytic results clearly showed a decrease in activity when increasing the alkyl chain length of the olefin. For example, β-CD/1-alkene complexes for which the alkene contains more than ten carbons had a pronounced hydrophobic character due to the non-included moiety of the substrate alkyl chain. The substrate cannot be properly recognized by a single CD cavity and the reaction with the water soluble catalyst was consequently disfavored. We showed that β-CD residues grafted on size-controlled poly(*N*-acryloyloxysuccinimide) (polyNAS) could act as hydrophobic pocket for the cooperative recognition of very hydrophobic substrates (Fig. 6) [57].

While the utilization of RAME-β-CD was limited to olefins containing 8 or 10 carbons, the β-CD-based polyNAS allowed for the effective hydroformylation of olefins containing up to 16 carbons (Fig. 7) without detrimental effect on the aldehydes selectivities and the linear to branched aldehyde product ratios.

2.2.3 Cyclodextrin-Mediated Interfacial Catalysis

Knowing that the reaction is under mass transfer control does not indicate the role of the CDs in the catalytic process. The precise role of the CDs was established by careful analysis of experimental data and molecular dynamics simulations. Some of the results obtained are discussed below.

In water, inclusion complexation is a highly dynamic process in which the CD and the olefin undergo association and dissociation at relatively fast rates. The association constants K_a between the CDs and the substrates were long held

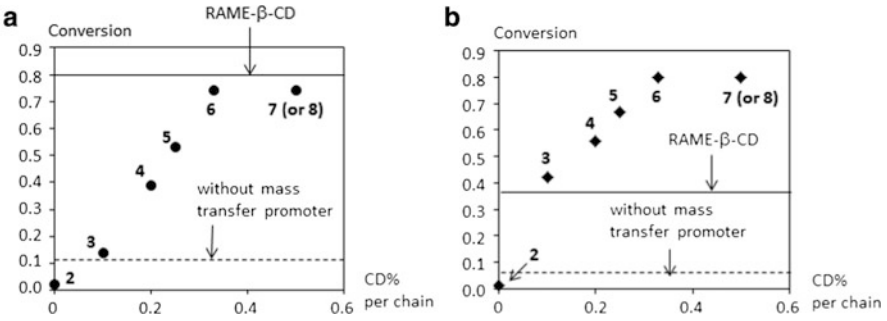


Fig. 7 Conversion of 1-decene (**a**) and 1-hexadecene (**b**) vs CD percentage on the polymer chains. See Fig. 6 for the values of CD percentages on the polymer chains. Catalytic conditions: substrate (1.63 mmol), $Rh(CO)_2(acac)$ (0.012 mmol), TPPTS (0.058 mmol), additive (calculated for 0.116 mmol equiv. CDs), 6 mL H_2O, 80°C, 50 bar CO/H_2. Reprinted with permission from [57]. Copyright (2012) American Chemical Society

Table 4 Association constant K_a (M^{-1}) between CDs and reactants or products[a]

CD	1-Octene	1-Decene	1-Dodecene	Undecanal	2-Methyl decanal
RAME-β-CD	76	123	180	1,198	1,167
RAME-α-CD	188	296	470	945	336
HP-β-CD	36	66	78	698	310
HP-α-CD	48	76	90	214	110
β-CD	84	164	230	412	n.d.[b]
α-CD	249	468	516	393	n.d.[b]

[a]Formation constants were determined by static headspace gas chromatography at 80°C [58]
[b]Not determined

responsible for the variation of the initial activities depending on the length of the olefinic chain or the nature of the CD. It has recently been proved by a static headspace technique that the initial activity was not linked to the strength with which CDs and olefins interact. In Table 4 some of the interesting K_a values for CD/olefin couples are summarized. It seems clear that the K_a values were higher when the olefinic chain was longer, and higher for α-CDs than for β-CDs.

In the light of Table 4, the catalytic results could be compared and explained. Increasing the alkyl chain length resulted in a drop of activity [52]. For example, after 6 h at 80°C under 50 bar CO/H_2 (1/1 mixture) with RAME-β-CD as mass-transfer promoter, 100% of 1-decene were converted when only 64% of 1-dodecene had reacted. This result was inconsistent with the hypothesis that a higher K_a value led to a higher activity since the RAME-β-CD/1-decene association constant was smaller than the RAME-β-CD/1-dodecene association constant (123 M^{-1} vs 180 M^{-1}). Moreover, the RAME-α-CD/1-decene association constant was more than twice that of the RAME-β-CD/1-decene supramolecular complex when the relative reaction rate measured with RAME-β-CD was twice that measured with RAME-α-CD. Thus, the stability of the CD/substrate inclusion complex did not reflect the CD activity.

The precise role of modified CDs in the hydroformylation reaction has been clarified by Sieffert and Wipff using molecular dynamics simulations [59, 60]. They have investigated the interfacial distribution of partners involved in the rhodium catalyzed hydroformylation of olefins promoted by native β-CD and the 2,6-dimethyl-β-cyclodextrin (DIME-β-CD). Their work indicated that DIME-β-CD and its inclusion complexes with 1-decene, undecanal, or the key reaction intermediate [RhH(CO)$(TPPTS)_2$(decene)] were all surface-active and preferred the aqueous/organic interface over the bulk aqueous phase. In contrast to [RhH(CO)$(TPPTS)_3$], it was also found that the catalyst "active" forms [RhH(CO)$(TPPTS)_2$] or [RhH(CO)$(TPPTS)_2$(decene)] also preferred the interface over the bulk aqueous phase. In fact, these molecular dynamics simulations suggested that CDs did not act as "shuttles" transferring the hydrophobic olefin into the aqueous phase but as surface active receptors promoting the meeting of the organometallic catalyst and the olefin at the aqueous/organic interface. Interestingly, it was also proposed that one advantage of using methylated CDs instead of native CDs was that the former adopt specific amphiphilic orientations at the interface, with the wide rim pointing towards the water phase, and this orientation was suitable for the formation of inclusion complexes with the reactant or the key reaction intermediate [RhH(CO)$(TPPTS)_2$(decene)]. Furthermore, it was also observed that the TPPTS sulfonate groups of [RhH(CO)$(TPPTS)_2$(decene)] could interact "facially" with DIME-β-CD by forming hydrogen bonds with the CD hydroxyl groups (Fig. 8). Finally, two important features emerged from the analysis of the different CD complexes at the interface: the CD pre-organized the alkene substrate for the reaction to occur with the Rh-complex and better interacted with the reaction intermediate than with the reactant, pointing to the analogy with enzyme-catalyzed systems.

As Wipff's work suggested that the key point of the CD based hydroformylation processes was adsorption of CDs at the interface, the behavior of various native or modified α- and β-CDs at the air-water interface was deeply investigated by surface tension measurements (Fig. 9) [61]. The surface tension measurements confirmed that chemically modified CDs adsorb at the air-water interface and allowed one to determine surface excess of CD (i.e., CD concentration adsorbed at the interface) using the Gibbs adsorption equation. Interestingly, a good correlation between surface excess and catalytic activity was obtained in 1-decene hydroformylation (Fig. 10).

This correlation fully supports the fact that the 1-decene hydroformylation occurred at the interface as initially suggested by molecular dynamics simulations. Indeed, the higher the CD concentration at the interface, the higher the catalytic activity. Therefore, contrary to what was initially proposed [24, 54], it can now be considered that the reaction does not take place in the bulk water for higher olefins but at the liquid–liquid interface where all partners of the catalytic process are concentrated. The two mechanisms proposed for the CD-based hydroformylation processes are represented in Fig. 11.

To improve the performances of the biphasic system, modified CDs have been designed to favor their adsorption at the interface. As such, modified CDs

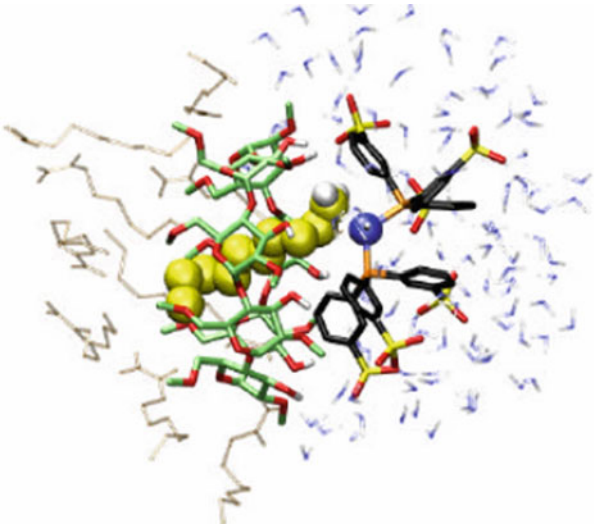


Fig. 8 [RhH(CO)$(TPPTS)_2$(1-decene)]/DIME-β-CD complex adsorbed at the 1-decene/water interface. This structure was generated by a molecular dynamics simulation. Reproduced with permission from [60]. Copyright Wiley-VCH Verlag GmbH & Co.

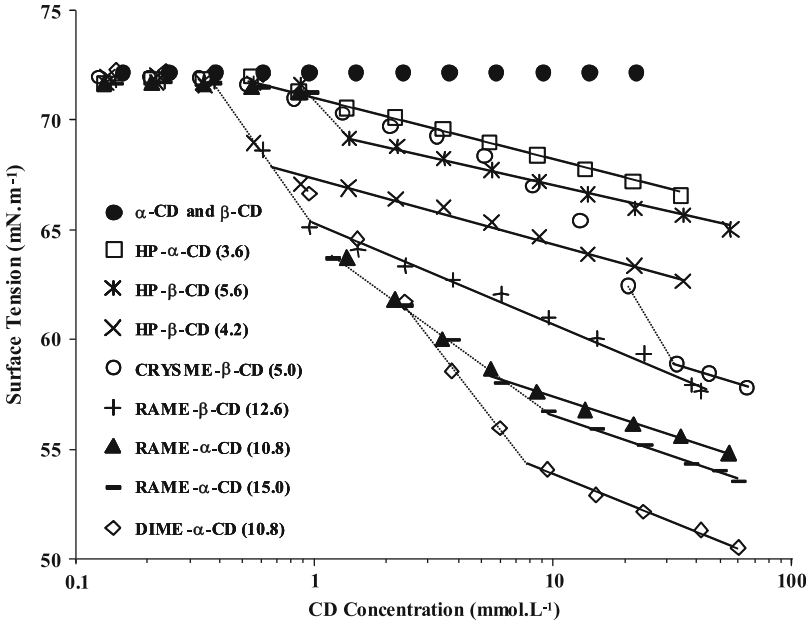


Fig. 9 Surface tension vs CD concentration at 25°C

sulfoalkylated on their primary face and alkylated on their secondary face (n-α-n′ or n-β-n′) have been synthesized by Green and coworkers [49, 62]. The activities obtained with these CDs were higher than those measured with partially methylated

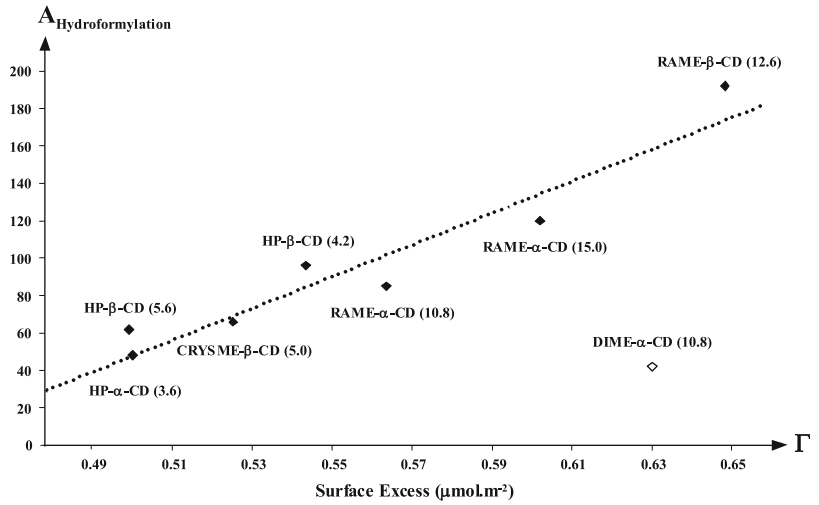


Fig. 10 CDs catalytic activity (A) in 1-decene hydroformylation vs surface excess (Γ) [$A = 856.9 \times \Gamma$ (μmol m^{-2}) $- 379.2$; $R^2 = 0.9180$]

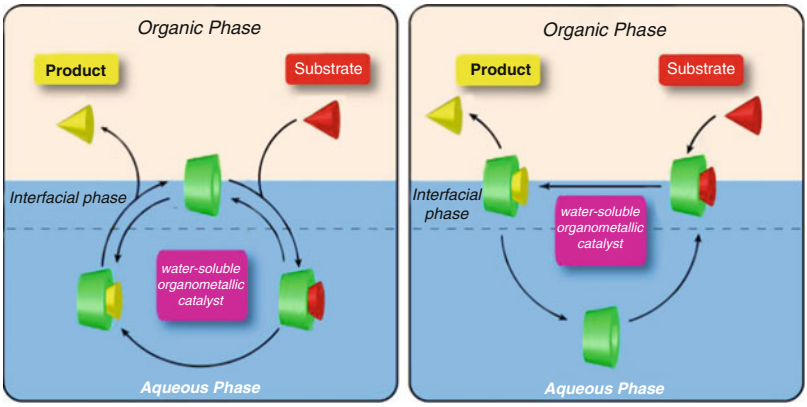


Fig. 11 Mechanism proposed for CD-based hydroformylation processes. (**a**) In the case of lower olefins, the hydroformylation reaction mainly occurs in the aqueous bulk phase (inverse phase transfer catalysis). (**b**) For case of higher olefins such as 1-decene, the hydroformylation reaction essentially occurs in the interfacial layer (interfacial catalysis)

or hydroxypropylated CDs while those obtained with native or permethylated CDs gave very modest results (Table 3). Their marked amphiphilic character, which was a consequence of their well-defined hydrophobic and hydrophobic parts, gave them a huge advantage over other CDs to adsorb at the interface. Note that the highest activities in Rh-catalyzed 1-decene hydroformylation were measured with 4-β-n′ (more than 250-fold increase in relative reaction rate over that measured without CD). However, an unconsidered lengthening of the CD amphiphilic structure had

Fig. 12 Coordination–decoordination equilibrium of TPPTS between the non-active [RhH(CO)$(TPPTS)_3$] and active [RhH(CO)$(TPPTS)_2$] species

detrimental effect on the phase separation. Thus, in contrast to 4-β-1 (β-CD sulfobutylated on its primary face and methylated on its secondary face), 4-β-2 gave stable microemulsions, preventing an easy recovery of the catalytic system (Blach P, Fourmentin S, Bricout H, Monflier E, unpublished results).

2.2.4 Influence of the TPPTS Concentration

The effect of the TPPTS concentration was investigated at constant rhodium concentration and constant RAME-β-CD/Rh ratio [54]. The relative reaction rate markedly decreased with the amount of TPPTS due to the increase in the solution ionic strength. The influence of the ionic strength was crucial as it strongly increased the interfacial tension (salting-out effect). This indirectly corroborated the interfacial character of the catalytic process. The drop in activity when increasing the TPPTS concentration was also a consequence of the shift in the equilibrium between [RhH(CO)$(TPPTS)_3$] and [RhH(CO)$(TPPTS)_2$] toward the inactive [RhH(CO)$(TPPTS)_3$] species (Fig. 12).

Finally, the decrease in activity was also due to the formation of inclusion complexes between TPPTS and RAME-β-CD. Indeed, when TPPTS was included within the CD cavity, the amount of free CD at the interface was reduced. Note that the formation of inclusion complexes between the CD and the TPPTS ligand has been evidenced by NMR [63], UV–vis spectroscopies [64], and scanning tunnelling microscopy [65]. For instance, two dimensional NMR experiments have demonstrated that a TPPTS aromatic ring was included within the hydrophobic RAME-β-CD cavity as intense cross-peaks between the inner protons of RAME-β-CD (H-3 and H-5) and the aromatic protons of TPPTS were observed on a 2D T-ROESY spectrum of a RAME-β-CD/TPPTS mixture. An 840 M^{-1} association constant was measured between them. Note that the interaction between TPPTS and RAME-β-CD was also evidenced by ^1H diffusion-ordered NMR spectroscopy experiments [66]. Thus, a large decrease in TPPTS diffusion coefficient was measured by the PGSE-NMR technique on RAME-β-CD/TPPTS mixtures (Fig. 13).

2.2.5 The Case of Modified α-CDs

Even though the interfacial character of the Rh-catalyzed hydroformylation has now been demonstrated and is well accepted, some intriguing results have been observed with modified α-CDs [67]. With 1-octene as substrate, RAME-α-CD was more efficient than RAME-β-CD (Table 3). HP-α-CD, for its part, was one half less

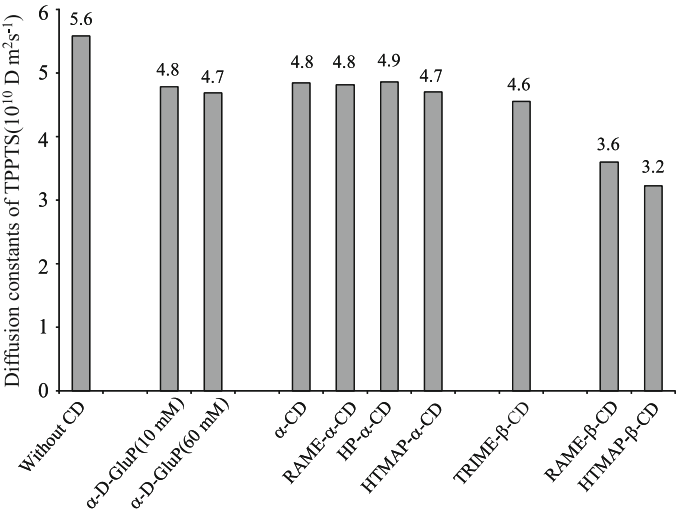


Fig. 13 Diffusion coefficient of TPPTS (10 mM) in the presence of various CDs (10 mM) determined by PGSE-NMR technique. Control experiments were also performed with methyl-α-D-glucopyranoside (α-D-Glup), the constitutive building block of CDs

efficient than RAME-α-CD. Astonishingly, the results were different with 1-decene as substrate. Indeed, the RAME-β-CD was found to be much more efficient than RAME-α-CD (Table 3). Moreover, the activity obtained with RAME-α-CD or HP-α-CD levelled-off after 6 h (Fig. 14).

Problems with α-CDs have already been mentioned by Jackson et al. during 1-hexene hydroformylation using $[RhH(CO)(TPPMS)_3]$ as catalyst precursor (TPPMS: m-monosulfonated triphenylphosphine sodium salt) [37]. The origin of the loss in activity is unclear at this point. Several hypotheses have emerged. First, an interaction of α-CDs with TPPTS was anticipated but our NMR measurements clearly showed that no internal (2D T-ROESY) or external (DOSY) interaction takes place between both compounds (see Fig. 13 for PGSE-NMR experiments). Second, an enzyme-like poisoning of the system by a too high association between the reaction products (undecanal and 2-methyldecanal) and CDs can be discarded since the association constants are lower for RAME-α-CD or HP-α-CD than for RAME-β-CD (Table 4). Third, the phenomenon might be related to an interaction between modified α-CDs and the catalytic organometallic species but for the moment this was not borne out even by high pressure NMR experiments.

2.2.6 Effect of Chemically Modified Cyclodextrins on Regioselectivity

Concurrently with what has been observed for biphasic system activity, the performances of rhodium-catalyzed hydroformylation have also been evaluated in terms of regioselectivity. Industrially speaking, linear aldehydes are preferred as

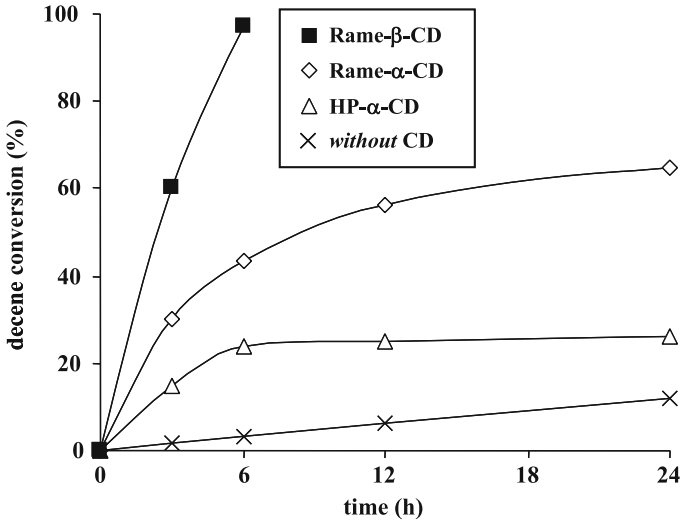


Fig. 14 1-Decene conversion as function of reaction time for different CDs. Experimental conditions: $Rh(acac)(CO)_2$: 0.041 mmol, TPPTS: 0.21 mmol, CD: 0.48 mmol, 1-decene: 20.35 mmol, water: 11.5 mL, 50 bar CO/H_2, *T*: 80°C

they are converted into plasticizers, lubricants, detergents, etc. To evaluate the linear aldehydes proportion, linear to branched aldehydes ratios (*l*/*b* ratio) have been calculated and compared. As can be seen in Table 3, the *l*/*b* ratio values are very dependent on the nature of the CDs. In particular, the decrease in *l*/*b* ratio measured when modified β-CDs such as RAME-β-CD or HP-β-CD were used as mass transfer promoters has long been unexplained. The problem has been solved using high pressure NMR Spectroscopy [68]. Indeed, the high pressure $^{31}P\{^1H\}$ NMR spectra reveal that, under 50 atm CO/H_2 at 80°C, RAME-β-CD strongly affects the equilibria between the various water-soluble rhodium species. The formation of an inclusion complex between RAME-β-CD and TPPTS was found to be the key to understanding the displacement of the equilibria between the rhodium species. It has actually been proved that TPPTS, which is initially added to the system or which results from a decoordination of an Rh-complex, is trapped by RAME-β-CD, inducing the formation of phosphine low-coordinated Rh-species (Fig. 15). Knowing that detailed studies on the $[RhH(CO)(TPPTS)_3]$ hydroformylation catalyst systems established that the two key catalytic species leading to linear and branched aldehydes are $[RhH(CO)(TPPTS)_2]$ and $[RhH(CO)_2(TPPTS)]$, respectively, the decrease in *l*/*b* ratio becomes understandable.

Several solutions have been developed to overcome the *l*/*b* aldehydes ratio drop. Modified α-CDs were considered simple and efficient molecular receptors to preserve the intrinsic properties of the Rh/TPPTS catalytic system since TPPTS proved unable to interact with their too narrow cavity [67]. Unfortunately, the unexplained deactivation of the catalytic system observed in the case of 1-decene

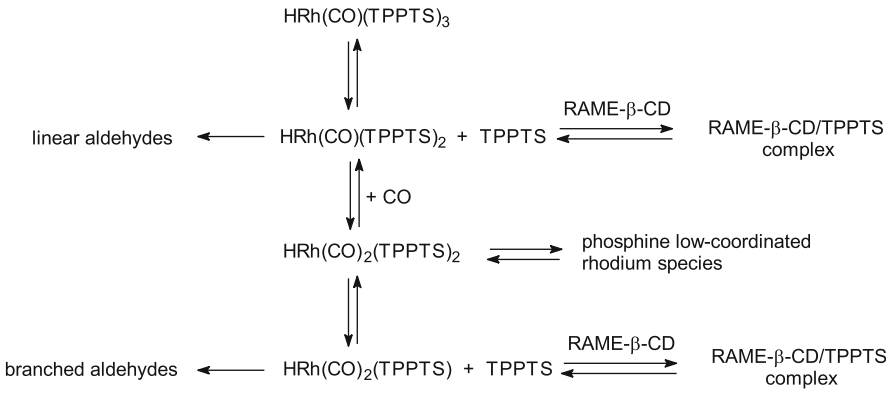


Fig. 15 Shifts in the rhodium species equilibriums due to the RAME-β-CD/TPPTS complex formation

hydroformylation (see Sect. 2.2.5 The case of modified α-CDs) indicates that the problem cannot be easily solved by the use of α-CD derivatives.

Improvements in the *l*/*b* ratio can also be realized by means of cationic CDs bearing 2-hydroxy-3-trimethylammonio-*n*-propyl groups (HTMAP) [48]. Indeed, *l*/*b* ratios up to 3.6 were measured, indicative of the in situ formation of new catalytic supramolecular species obtained by ion-exchange between the catalyst ligand and HTMAP. In contrast to supramolecular catalysts where the CD is coordinated to the catalysts [69–76], ionic bonding of CD to the organometallic catalyst offers the advantage of a reversible interaction with the catalyst. Consequently, when the CD is used in large excess with respect to the catalyst, the binding of the substrate–CD inclusion complex to the catalyst is transient and CDs could behave as supramolecular shuttles between the catalytically active center and the bulk or interface as schematically represented in Fig. 16.

Anionic CDs sulfoalkylated on their primary face and alkylated on their secondary face also act as efficient mass transfer promoters since the regioselectivity of the catalytic system was found to be identical to that observed without a mass transfer promoter [49, 62]. In fact, the presence of sulfonates and methyl groups on the CD repels the water soluble ligand, thus avoiding TPPTS trapping. The best result in regioselectivity is obtained using 3-β-1 (β-CD sulfobutylated on the primary face and methylated on the secondary face) since no significant variation of *l*/*b* was measured when compared to the reaction performed in the absence of CD. The accessibility to the CD secondary face appears to be determining in the catalytic process as it governs the approach between the CD-included substrate and the water-soluble catalyst.

2.2.7 Effect of Chemically Modified Cyclodextrins on Chemoselectivity

Nowhere apart from in hydroformylation chemoselectivity is there a more crucial need for an accurate design of the structure of the mass transfer promoter. As clearly visible in Table 3, the highest selectivities in aldehydes were obtained with

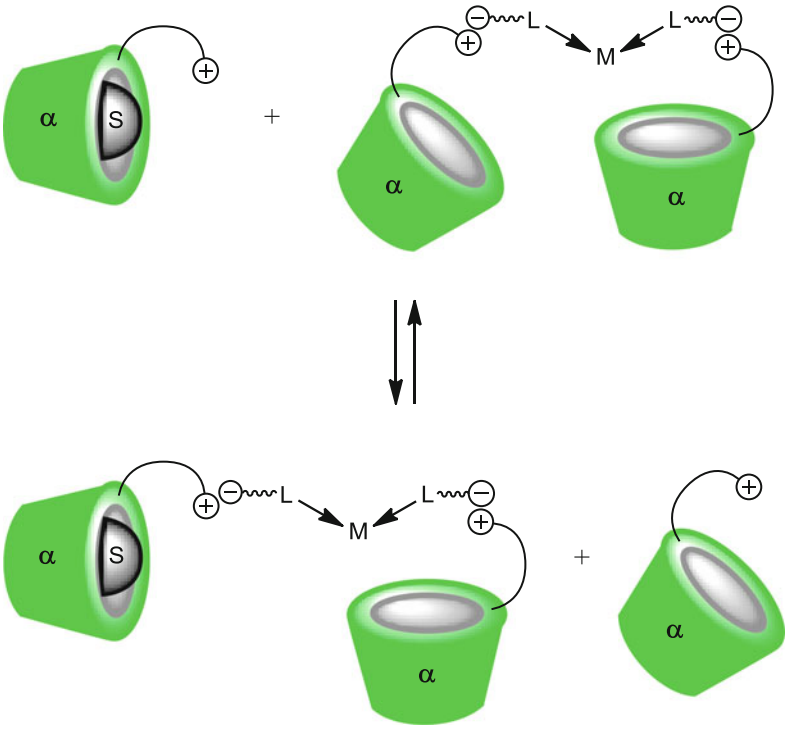


Fig. 16 Principle of supramolecular catalysis conducted in the presence of α-CD non-covalently connected to catalytic species. S = substrate; L⊖ = TPPTS

partially methylated CDs (92–98% aldehydes). Native CDs give modest results (80% aldehydes) when permethylated TRIME-β-CD, n-β-n′, or n-β-n′ give important amounts of internal olefins (around 40%). Furthermore, an accurate analysis of the catalytic results tends to demonstrate that the size of the CD cavity (α or β) and its extension by methyl or ethylated groups (4-β-1, 4-β-2) have little influence on the chemoselectivity. Therefore, contrary to what was initially proposed [24, 48], the protecting role of the cavity regarding the olefin to avoid isomerization can now be discarded.

In fact these results shed light on an essential feature of CDs as promoters in the hydroformylation reaction. Not only do CDs permit preorganization of the substrate and specificity in the recognition process, but subsequent action by the organometallic catalyst is also critically dependent on the presence of CD hydroxyl groups. Indeed, permethylation of the CD secondary face results in a dramatic decrease in the chemoselectivity, suggesting the essential role of the CD hydroxyl groups in the orientation of the reaction. A hydrogen bond between the CD hydroxyl groups and the phosphine of the organometallic catalyst is believed to occur. No spectroscopic evidence has ever been found but Wipff et al. demonstrated a possible hydrogen bond interaction between the CD and the sulfonates of the ligand by a molecular

dynamics simulation [59, 60]. Thus, the local environment around the metal is of great importance and the above hydrogen bond interaction is believed to favor insertion of carbon monoxide into the Rh-C bond rather than the β-elimination reactions responsible for isomerization processes.

2.3 CDs and Other Water-Soluble Ligands

2.3.1 Non-amphiphilic Ligands

The utilization of a partially methylated CD/alkyl-sulfonated diphosphine combination has been explored in Rh-catalyzed hydroformylation of 1-decene [77]. DPPETS, DPPPTS, and DPPBTS (Fig. 17) form inclusion complexes with β-CDs but were found to be unable to interact with α-CDs. The highest catalytic activities were observed with DPPBTS. In that case, a 15-fold increase in the catalytic activity was measured in the presence of RAME-α-CD and a 35-fold increase was obtained in the presence of RAME-β-CD when compared to a catalytic system without any CD. However, while increasing the conversion and the chemoselectivity, the *l*/*b* ratio dramatically decreases due to the formation of low-coordinated phosphine catalytic species. In fact, in order to reduce steric hindrance around the metal center, a mono-dissociation of the bidentate seemed to occur when the CD/1-decene inclusion complex approaches the rhodium center (Species A in Fig. 18). This mono-dissociation is attributed to the great flexibility of the alkyl chain linking the two diphenylphosphino groups. With RAME-β-CD, the phenomenon is accentuated since one of the two diphenylphosphino groups could be trapped by the CD leading to the formation of a second coordination sphere (Species B in Fig. 18) [78].

More recent work has provided salient results for assessing binding affinity of hindered phosphines for CDs and their influence on the hydroformylation of higher olefins. For example, the potential of sulfoxantphos (Fig. 17) as ligand for a CD-based hydroformylation process has been investigated [79]. The ligand molecular architecture evidently affects substrate recognition properties. In addition to activity enhancement, increase in the linear to branched aldehydes ratio from 12 to 32 was measured in hydroformylation of 1-decene when RAME-α-CDs were used as mass transfer promoter. Similarly, the *l*/*b* ratio increased from 12 to 26 using RAME-β-CD. Improvement of the regioselectivity resulted from two combined effects. First, contrary to what was observed with TPPTS and alkyl-sulfonated diphosphine, the interactions between the sulfonated xantphos and the methylated CDs were too weak to induce dissociation of the ligand from the complex under hydroformylation conditions. Second, concurrently with the constraint generated by the bulky sulfoxantphos ligand, the additional steric stress of the CD cavity on the substrate compelled the latter to react preferentially by its terminal carbon, leading to very high regioselectivity toward linear aldehyde (Fig. 19).

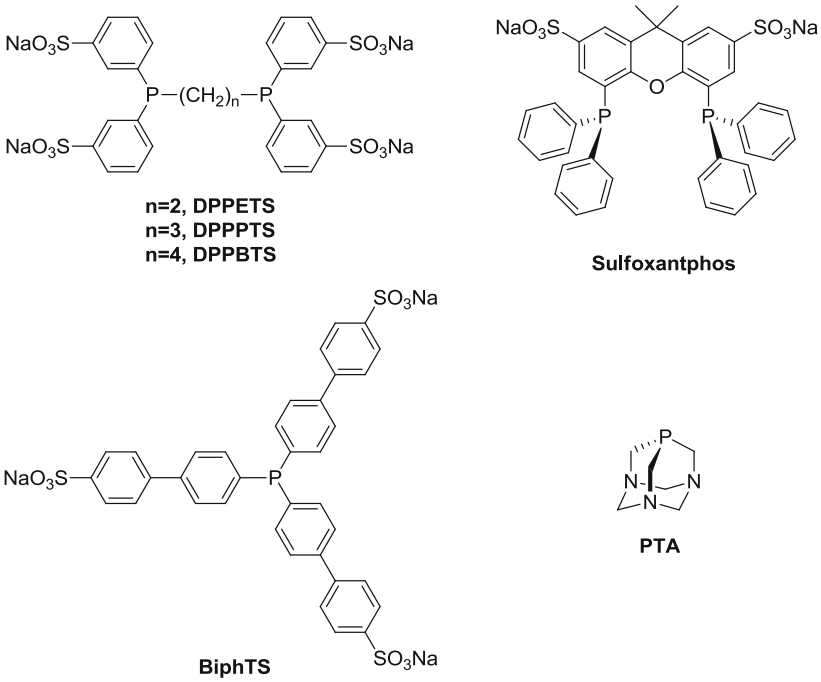


Fig. 17 Non-amphiphilic phosphines used in biphasic hydroformylation

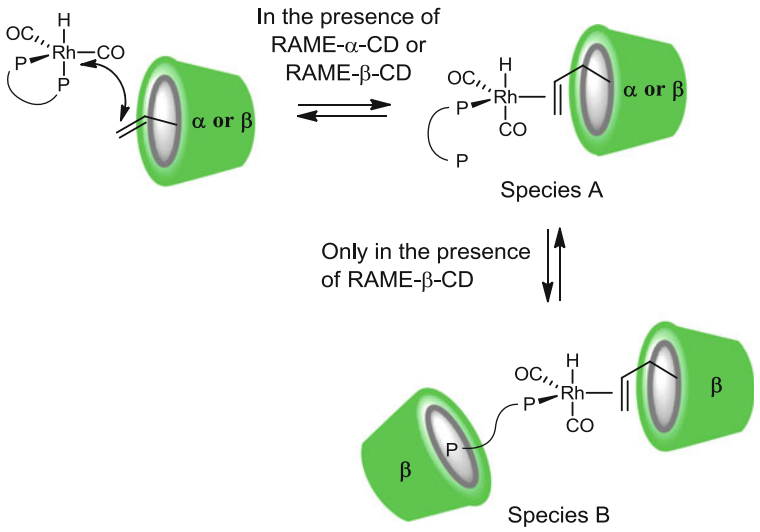


Fig. 18 Proposed mechanism for the decrease in *l*/*b* aldehydes ratio during the hydroformylation catalyzed by a rhodium/sulfonated alkyl diphosphines system

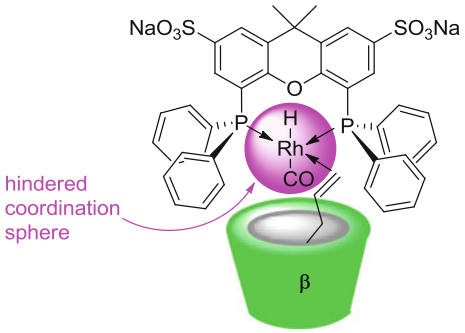


Fig. 19 Preferential insertion of the alkenyl terminal carbon in the crowded environment of the Rh-complex

Using tris(*p*-sulfonatobiphenyl)phosphine trisodium salt (BiphTS) as a ligand (Fig. 17), the conversion and the aldehydes selectivity were found to be strongly dependent on the phosphine/Co ratio, indicating that the BiphTS ligand coordinates more strongly to Co species than TPPTS [80].

The ability of PTA (PTA = 1,3,5-triaza-7-phosphaadamantane, Fig. 17) to stabilize Rh-species in water was also investigated. In contrast to most ligands described above, PTA could be considered as a non-interacting phosphine with respect to RAME-β-CD as clearly revealed by UV–vis and NMR spectroscopies [81]. In Rh-catalyzed hydroformylation reaction of 1-decene using RAME-β-CD as additive, PTA proved to a be poor ligand in terms of catalytic activity as a reaction temperature of 120°C was required for an 81% conversion to be obtained after 6 h under 50 bar CO/H_2. However, a comparison with TPPTS highlighted the beneficial effects of PTA on the chemoselectivity. Actually, chemoselectivities in aldehydes obtained with PTA were very high (>98%) whatever the temperature. Moreover, in contrast to what was observed with TPPTS, no decrease in regioselectivity was noticed as the linear to branched aldehydes ratio remained constant ($l/b = 1.9$).

2.3.2 Amphiphilic Ligands

As observed for PTA (see above), the *N*-benzylated PTA derivative (N-Bz-PTA)Cl (Fig. 20) also did not interact with RAME-β-CD [81]. However, its amphiphilic character allowed for a substantial increase of the catalytic performances especially the activity. In Rh-catalyzed hydroformylation of 1-decene under 50 bar CO/H_2, 86% conversion was obtained after 6 h at 100°C. The chemoselectivity was high (96%) but the regioselectivity rather poor (l/b ratio = 1.8).

When compared to TPPTS, the conversions obtained with *m*-TPPTC (Fig. 20) in Rh-catalyzed olefins hydroformylation were notably higher (increased by a factor of 47, 21, and 16 for 1-octene, 1-decene, and 1-dodecene, respectively) [82]. The surface activity of *m*-TPPTC might be responsible for its higher efficiency in the hydroformylation reaction. Interfacial tension measurements performed with *m*-TPPTC and TPPTS clearly revealed two different behaviors: TPPTS is a hydrotropic compound whereas *m*-TPPTC behaves as a surface active compound. With

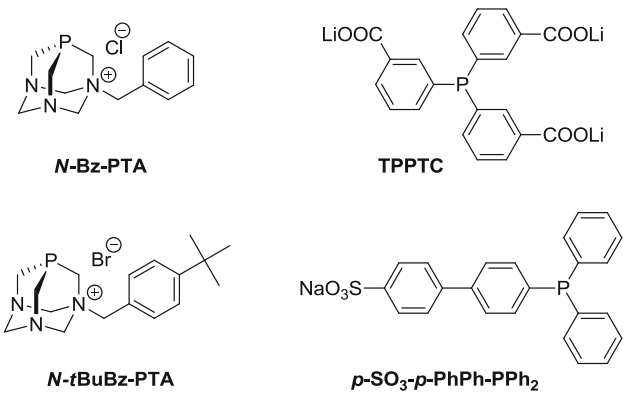


Fig. 20 Amphiphilic phosphines used in biphasic hydroformylation

TPPTC as ligand, *l*/*b* decreased in the presence of both partially methylated α- and β-CDs though only RAME-β-CD was able to trap TPPTC. As the *l*/*b* ratio decrease has been attributed to the formation of inclusion complexes between the ligand and the CD (see above), this phenomenon with RAME-α-CD and TPPTC is clearly unexpected. One way to explain this result could be a CD-induced decoordination process during the coordination of the RAME-α-CD/olefin inclusion complex on the rhodium center to reduce steric hindrance around the metal. In fact, the difference in behavior between TPPTC and TPPTS could be due to a different solvation sphere for the $[RhH(CO)(L)_2]$ species (L: TPPTS or TPPTC). Indeed, Hanson et al. explained the high regioselectivity of $[RhH(CO)(TPPTS)_3]$ in hydroformylation reactions by assuming that the loss of TPPTS from $[RhH(CO)(TPPTS)_2]$ is unfavorable due to a considerable reorganization of the solvation sphere [83]. In the case of TPPTC, it could be imagined that decoordination of a TPPTC ligand does not require an important solvation sphere reorganization and, consequently, a dissociation of one TPPTC ligand from the rhodium center could occur during coordination of the RAME-α-CD/olefin inclusion complex to reduce steric hindrance around the metal.

We recently demonstrated that the CD/PTA derivative combination could be of interest in a thermoregulated Rh-catalyzed hydroformylation of higher olefins. More precisely, a biphasic catalytic system has been elaborated in which the amphiphilic species concentrations at the aqueous/organic interface could be thermocontrolled by the supramolecular interaction between β-CDs and an appropriate ligand, namely the 1-(4-*tert*-butyl)benzyl-1-azonia-3,5-diaza-7-phosphaadamantyl ligand (*N*-*t*-BuBz-PTA, Fig. 20) [84]. An increase in the catalytic activity was observed without alteration in either the chemo- or the regioselectivity. In that case, the main advantage of the CD/phosphine couple lies in the rapid decantation of the biphasic system at the end of the reaction (Fig. 21).

Additionally, we also showed that the addition of ionic β-CDs in stoichiometric proportions into an amphiphilic phosphine-containing micellar solution (*p*-SO_3-*p*-PhPh-PPh_2, Fig. 22) unexpectedly improved the performances of the Rh-catalyzed

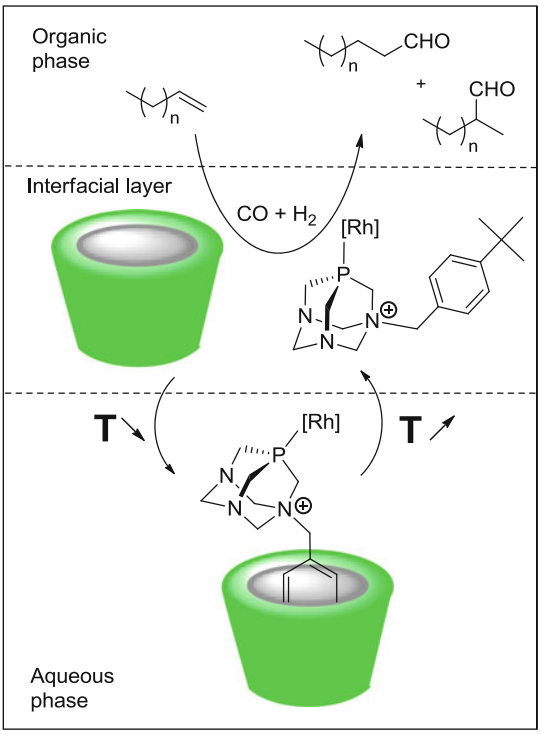


Fig. 21 CD-mediated thermocontrolled Rh-catalyzed hydroformylation of higher olefins

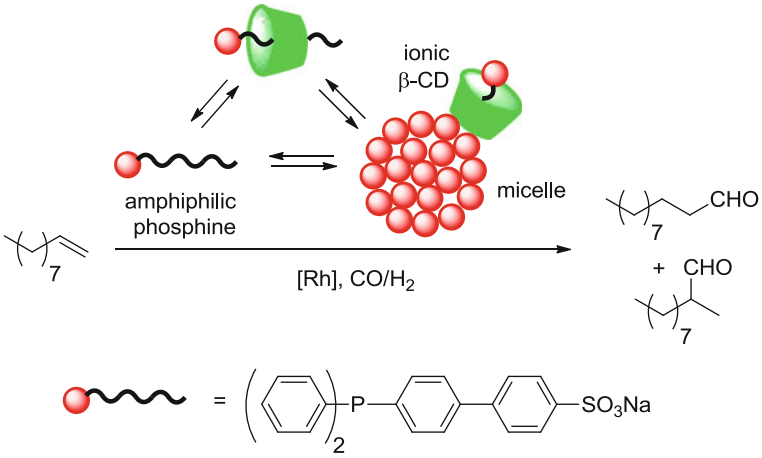


Fig. 22 Possible interactions between ionic β-CDs and an amphiphilic sulfonated phosphine in the micellar hydroformylation of 1-decene

hydroformylation of 1-decene in which complementary properties of the ligand and the surfactant were expressed in a single material [85]. The chemoselectivity was very high (>98% aldehydes) and an average fourfold increase in the catalytic

activity was obtained without detrimental effect on the regioselectivity. Moreover, the catalytic system could easily be recovered by simple decantation at the end of the reaction when randomly methylated β-CDs were used as additives.

3 Calixarenes as Molecular Receptors

3.1 Calixarenes: A Short Description

Calixarenes are organic macrocycles built up from phenolic groups held together by methylene groups (Fig. 23) [86]. They are characterized by a wide upper rim and a narrow lower rim. They can be substituted at the *para*-position on the aromatic rings and/or on the hydroxyl groups. In contrast to CDs for which only the cavity is hydrophobic, non-substituted calixarenes are fully hydrophobic and should be modified by hydrophilic substituents to be used in aqueous media. Their utilization as molecular receptor in catalysis has been the subject of numerous publications, especially in organic solvents [87, 88]. However, studies on their utilization in water are few [89]. Below are detailed the main results obtained with functionalized calix[*n*]arenes in aqueous biphasic hydroformylation of alkenes.

3.2 Functionalized Calix[n]arenes as Molecular Receptors

Though sparse, the utilization of functionalized calix[*n*]arenes in biphasic hydroformylation of alkenes led to promising results. For example, *p*-sulfonato-calix[4]arenes (Fig. 24, R = H) proved to be effective under 5–30 bar CO/H_2 at 70°C using a toluene/water mixture in Rh/TPPTS-catalyzed hydroformylation of 1-heptene, 1-octene, and 1-nonene [90]. However, nothing was said about the real catalytic activity of the system. Moreover, the isomerization percentage (from 20% to 60%) was high whatever the substrate and no clear explanation was given for the results obtained from the calixarene structure. Though the calixarenes' cavity is believed to include a substrate, no spectroscopic evidence certified the existence of supramolecular complexes in the reaction media.

Upper rim-*t*-Bu calix[4]arenes could be used as molecular platform to access neutral calix-diphosphite rhodium complexes (Fig. 24) [91]. Their catalytic activity has been evaluated in the micellar hydroformylation of 1-octene, 1-hexene, and styrene at 50°C under 20 bar CO/H_2. In water and without any surfactant, a biphasic system was obtained, the Rh-catalyst being soluble in the organic phase. Conversely, when mixed in water with surfactants such as calix[4]arenes substituted on the upper rim by sulfonated groups and on the lower rim by alkyl chains (Fig. 24, R = C_nH_{2n+1} with *n*: 4, 6, or 8), the calix-diphosphite Rh-complex proved to be a very regioselective catalyst in micellar hydroformylation of 1-octene as linear/branched ratios up to 61.8 could be measured. Indeed, the formation of a

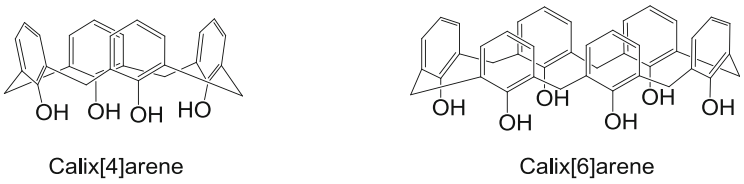


Fig. 23 Examples of calix[*n*]arenes

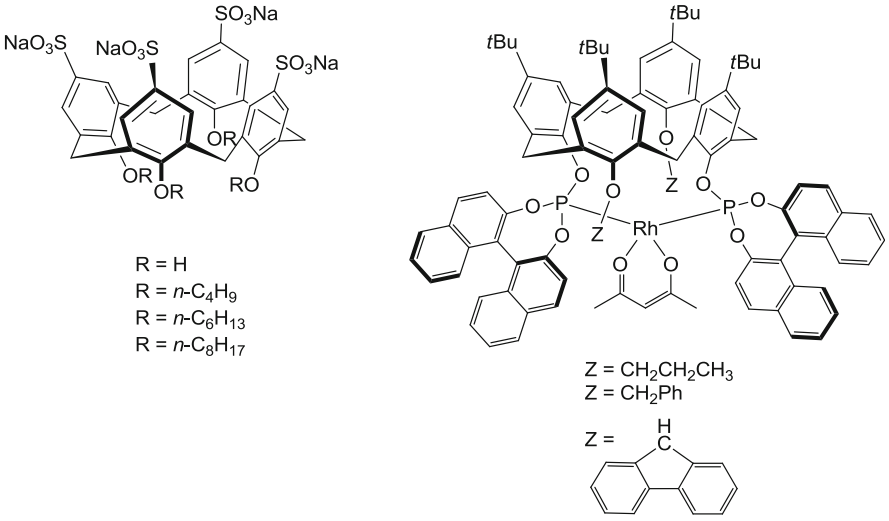


Fig. 24 Upper rim-sulfonated calix[4]arene (*left*) and calix-diphosphite Rh-complex (*right*) used in micellar hydroformylation of alkenes

microenvironment within the micelles confined the substrate in a tight hydrophobic pocket and forced the hydroformylation to occur preferentially on the terminal alkenyl carbon.

A water-soluble phosphite derived from sulfonated calix[4]arene has been recently synthesized that proved to be active in a two-phase (water/toluene) hydroformylation of 2-methylpentenoate [92]. Under 60 bar CO/H_2 at 160°C with a Rh-catalyst, branched aldehydes are the only products of hydroformylation and one of the branched aldehydes is selectively hydrogenated to give the lactone derivative. However, the stability of the calixarene-derived phosphite is questionable as a decomposition process was pointed out leading to H_3PO_3 and free sulfonated calixarenes.

Other work established that 1-octene could be converted into nonanals with high yields (up to 73%) and good regioselectivities (*l*/*b* from 1.7 to 3.5) using the upper rim functionalized calix[4]arenes described in Fig. 25 in the presence of [Rh(acac)$(CO)_2$] as precatalyst and with a 1:1 CO/H_2 mixture in water at 100°C and 40 bar for 12 h [93]. In the same catalytic conditions, the standard TPPTS/[Rh(acac)$(CO)_2$]

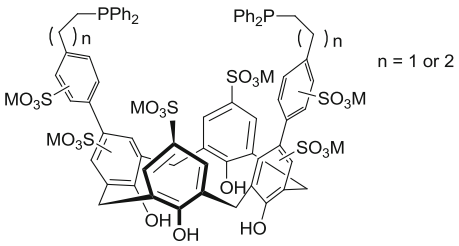


Fig. 25 Water-soluble calix[4]arenes synthesized by Shimizu and coworkers

gave a poor 21% conversion. One of these receptors (Fig. 25, $n = 2$) showed retention of catalytic ability and selectivity when recycled two or three times. It was also effective for the hydroformylation of dec-1-ene.

The utilization of these modified calix[4]arenes has been extended to internal olefins [94]. Good conversions were obtained in Rh-catalyzed hydroformylation of *trans*-4-octene, *cis*-4-octene, and *trans*-2-octene. Selectivities were similar to those obtained with a RAME-β-CD/TPPTS combination. The catalytic system could be recycled five consecutive times without loss of activity.

4 Conclusions

Since the first efficient application of a molecular receptor in rhodium-catalyzed hydroformylation of higher olefins (1991), a great deal of information has been collected and interpreted. While we still clearly have a long way to go in terms of fully defining their potential in biphasic catalysis, it is hoped that this chapter has highlighted the very substantial progress that has already been made to this end. It is well established now that molecular receptors such as CDs and calixarenes significantly favor the contact between the organometallic catalyst and the olefin at the interface or into the bulk aqueous phase according to the nature of the olefin.

Finally, in a broader context, the present findings lend strong support for the conclusion that the mass transfer properties of molecular receptors are much richer in complexity and more exploitable than has previously been considered. The art of synthesizing efficient molecular receptors and phosphines has been of tremendous help in the understanding of the catalytic process and now opens fascinating opportunities in the area of biphasic aqueous catalysis. For example, the formation of inclusion complexes between modified CDs and appropriate water soluble phosphines can be advantageously used to design new water soluble self-assembled supramolecular bidentates ligands for aqueous organometallic catalysis [95, 96].

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Asymmetric Hydroformylation

Bernabé F. Perandones, Cyril Godard, and Carmen Claver

Abstract Rhodium is currently the metal of choice to achieve high enantioselectivities in the hydroformylation of a relatively wide variety of alkene substrates. The elucidation of the different steps of the catalytic cycle and the characterization of the resting state, together with the discovery of several types of ligands that are able to provide high enantioselectivities, have made the rhodium-catalyzed hydroformylation a synthetically useful tool.

For years, ligands containing phosphite moieties such as diphosphites and phosphine–phosphites were considered the most successful ligands to achieve high enantioselectivities for classical substrates such as styrene and vinyl acetate. In fact, the phosphite–phosphine BINAPHOS (**43**) and its derivatives are still today the most successful ligands in terms of selectivity and scope. For more substituted substrates, general trends can be extracted. However, recent studies showed that these general trends can be sometimes reversed by the use of the appropriate catalyst and choice of reaction conditions, clearly showing that these trends are only indicative and that there are still many challenges to be tackled in this area.

Keywords Asymmetric · Chiral ligands · Enantioselectivity · Hydroformylation · Phosphine · Phosphite · Phosphorus · Regioselectivity · Rhodium

Contents

B.F. Perandones, C. Godard (✉), and C. Claver
Departament de Química Física i Inorgánica, Universitat Rovira i Virgili, C/ Marcel.li Domingo s/n, 43007 Tarragona, Spain
e-mail: cyril.godard@urv.cat

1 Introduction

The hydroformylation of alkenes, which was originally discovered by Otto Roelen in 1938 [1–3], is nowadays one of the most important industrial applications of homogeneous catalysis [4–12]. However, the potential of this process in fine chemicals production is still to be exploited.

From a synthetic point of view, the reaction is a one-carbon chain elongation caused by the addition of carbon monoxide and hydrogen across the π system of a C═C double bond [13, 14 and references therein]. As a pure addition reaction, the hydroformylation reaction meets all the requirements of an atom economic process [15]. Furthermore, the synthetically valuable aldehyde function is introduced, which allows subsequent skeleton expansion that may even be achieved in one-pot sequential transformations [16, 17].

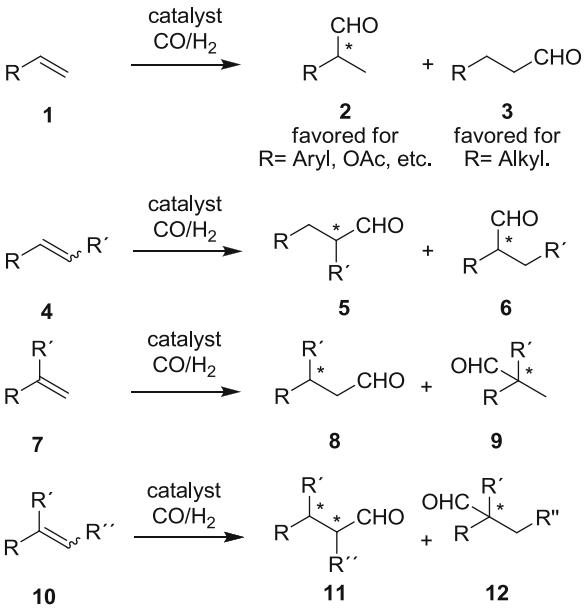
Since early studies, ligand modification of the rhodium catalyst has been the main strategy to influence the catalyst activity and selectivity [18–21 and references therein].

In the asymmetric hydroformylation of alkenes, the first examples of high level of enantioselectivity (ees up to 90%) were achieved by Stille and Consiglio using chiral Pt- diphosphine systems [22–24]. However, these catalysts suffered several disadvantages such as low reaction rates, tendency to hydrogenate the substrates, and low regioselectivity to the branched products.

Rhodium is currently the metal of choice to achieve high enantioselectivities in the hydroformylation of a relatively large variety of alkene substrates. The elucidation of the different steps of the catalytic cycle and the characterization of the resting state, together with the discovery of several types of ligands that are able to provide high enantioselectivities, have made rhodium-catalyzed hydroformylation a synthetically useful tool [25, 26].

In asymmetric hydroformylation of alkenes, the regioselectivity is key to providing chiral products and is a function of many factors. These include inherent substrate preferences, directing effects exerted by functional groups as part of the substrate, as well as catalyst effects. In order to appreciate substrate inherent regioselectivity trends, alkenes have to be classified according to the number and nature of their substituent pattern (Scheme 1) [13, 14 and references therein].

Scheme 1 Regioselectivity trends in the hydroformylation of various alkenes

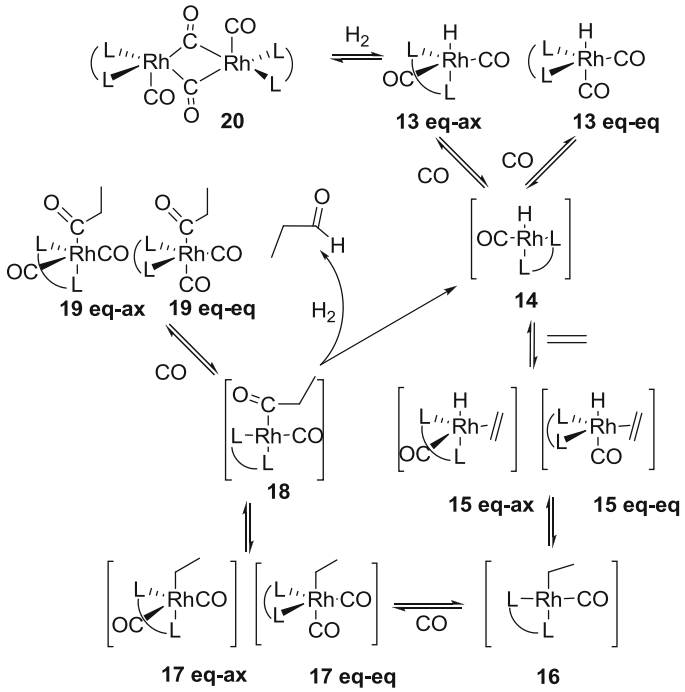


For the terminal alkenes **1** containing electron-withdrawing substituents, the formation of the branched product **2** is favored. The regioselectivity issue usually only arises for terminal and 1,2-disubstituted alkenes **4**, where isomerization usually leads to the formation of the linear products. For 1,1-disubstituted **7** and trisubstituted **10** alkenes, only one regioisomer is generally produced (**8** and **11**, respectively) with the formyl group being usually added so the formation of a quaternary carbon center is avoided [27].

However, recent studies showed that these general trends can sometimes be reversed by appropriate catalyst modifications and choice of reaction conditions, clearly showing that these trends are only indicative and that there are still many challenges to tackle in this area. Among the most significant issues are (1) the low reaction rates at low temperature where good selectivities are usually observed, (2) the difficulty to control simultaneously the regio- and the enantioselectivity, and (3) the limited substrate scope for any single ligand.

2 Rh-Catalyzed Hydroformylation Mechanism

In Scheme 2 the well accepted mechanism of the Rh-catalyzed hydroformylation proposed by Heck is described for bidentate ligands [28]. It corresponds to Wilkinson's so-called dissociative mechanism [18–20]. The associative mechanism involving 20-electron intermediates for ligand/substrate exchange will not be considered. In this process, a great understanding of the mechanism has been possible



Scheme 2 Mechanism of the Rh-catalyzed asymmetric hydroformylation in the presence of bidentate ligand (L–L)

due to the observation and structural characterization of the resting state of the catalyst by in situ spectroscopic techniques (HP-IR, HP-NMR) [21 and references therein]. For bidentate ligands (L–L), the common starting complex is the [RhH(L–L)$(CO)_2$] species **13**, containing the ligand coordinated in equatorial positions (denoted eq–eq throughout the scheme) or in an apical–equatorial position (complexes denoted eq–ax).

Dissociation of equatorial CO from **13** leads to the square-planar intermediate **14**, which associates with alkene to give complexes **15**, where the ligand can again be coordinated in two isomeric forms eq–ax and eq–eq, having a hydride in an apical position and alkene coordinated in the equatorial plane. On the basis of experimental results and theoretical calculations, it has been proposed that the regioselectivity is determined by the coordination of the alkene to the square planar intermediate **14** to give the pentacoordinate intermediates **15** [29]. This step is also crucial in determining the enantioselectivity since the enantioface discrimination occurs between **14** and **16**, and particularly between **14** and **15**. The CO dissociation from **13** was shown to be much faster than the overall hydroformylation process, indicating that the rate of the reaction is dominated by the reaction of **14** with either CO or the alkene to form **13** or **15** [30]. It has not been established experimentally whether alkene complexation is reversible or not, although in Scheme 2 all steps are

described as reversible except the final hydrogenolysis. Experiments using deuterated substrates suggest that alkene coordination and insertion into the Rh–H bond can be reversible, certainly when the pressures are low. Complexes **15** undergo migratory insertion to give the square-planar alkyl complex **16**. This species can undergo β-hydride elimination, thus leading to isomerization, or can react with CO to form the trigonal bipyramidal (TBP) complexes **17**. Thus, under low pressure of CO more isomerization may be expected. At low temperatures (<70°C) and sufficiently high pressure of CO (>10 bar) the insertion reaction is usually irreversible and thus the regioselectivity and the enantioselectivity in the hydroformylation of alkenes are determined at this point. Complexes **17** undergo the second migratory insertion (see Scheme 2) to form the acyl complex **18**, which can react with CO to give the saturated acyl intermediates **19** or with H_2 to give the aldehyde product and the unsaturated intermediate **14**. The reaction with H_2 presumably involves oxidative addition and reductive elimination, but for rhodium no trivalent intermediates have been observed [31]. At low hydrogen pressures and high rhodium concentrations, the formation of dirhodium dormant species such as **20** becomes significant [32].

As mentioned above, the catalytic hydroformylation of alkenes is one of the largest applications of homogeneous organotransition metal catalysis today. Due to the robustness of the process and the wide availability of alkene substrates, enantioselective hydroformylation provides high possibilities to obtain a great variety of enantiomerically pure aldehydes. The first Rh-based systems that were reported in the asymmetric hydroformylation contained diphosphine ligands that provided low to moderate enantioselectivities [25, 26]. With this type of ligand, the highest ee value was reported using styrene as substrate and bdpp (bis-diphenylphosphino pentane) as ligand (ees up to 64%) [33]. Later, higher enantioselectivities were achieved using more sophisticated diphosphite and phosphine–phosphite ligands [6–14 and references therein; 18–20].

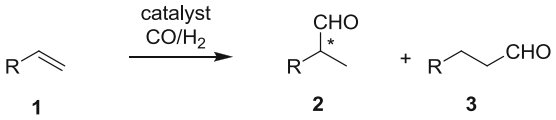
In the following sections, the most relevant results reported in the asymmetric Rh-catalyzed hydroformylation of alkenes are described. The reactions are classified by degree of substitution of the substrates in order to highlight the issue of the substrate/ligand compatibility in this process. Advances in supported chiral catalysts in this process are also described.

3 Rh-Catalyzed Asymmetric Hydroformylation of Monosubstituted Alkenes

The hydroformylation of monosubstituted alkenes (Scheme 3) was extensively studied due to the interest in the synthesis of linear aldehydes (non-chiral) or the enantioselective synthesis of 2-substituted branched aldehydes using chiral hydroformylation catalysts [4–14 and references therein].

For example, the hydroformylation of vinyl arenes (R = aryl) is used as a model for the synthesis of 2-aryl propionaldehydes, which are intermediates in the

Scheme 3 Asymmetric hydroformylation of monosubstituted alkenes



synthesis of 2-aryl propionic acids, the profen class of non-steroidal drugs. The Rh-catalyzed asymmetric hydroformylation of several other monosubstituted alkenes, such as allyl cyanide and vinyl acetate, was successfully carried out [6–14 and references therein]. In general, 1,3-diphosphite and phosphine–phosphite ligands provided the best results in these processes [18–20]. However, the use of bisphosphacyclic ligands has recently emerged as an efficient alternative [6–14 and references therein].

3.1 1,3-Diphosphite Ligands

The use of diphosphite ligands was intensively studied in this process as they provide high levels of selectivity with these substrates [34]. The initial success in the rhodium-catalyzed asymmetric hydroformylation of vinyl arenes came from Union Carbide with the discovery of the diphosphite ligand (2*R*, 4*R*)-pentane-2,4-diol **21** (Scheme 4) [35, 36].

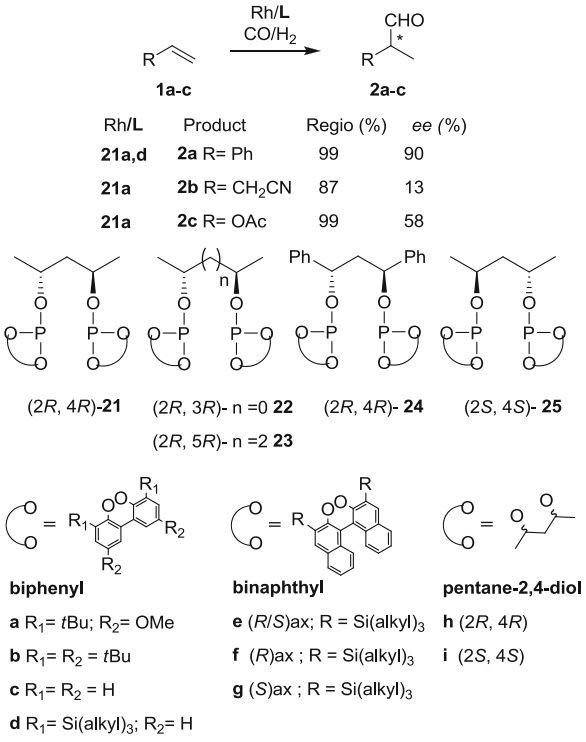
Good chemo-, regio-, and enantioselectivities (ee up to 90%) were obtained with (2*R*, 4*R*)-pentane-2,4-diol diphosphite derivatives (**21a–c**) but only when the reaction was performed around room temperature. Inspired by these excellent results, other research groups synthesized the series of diphosphite ligands **22–25** in order to study the effect of structural modifications on the Rh-catalyzed asymmetric hydroformylation of vinyl arenes (Scheme 4) [37–41].

The influence of the bite angle of these ligands was studied with diphosphite ligands (2*R*, 4*R*)-pentane-2,4-diol **21**, (2*R*, 4*R*)-butane-2,4-diol **22**, and (2*R*, 4*R*)-hexane-2,4-diol **23** [38]. In general, the ligand **21**, which contains a three-carbon-atoms bridge, provided higher enantioselectivities than ligands **22** and **23**, which have a two and four-carbon-atoms bridge, respectively.

The effect of different phosphite moieties was studied with ligands **21a–g** [37–39]. In general, sterically hindered phosphite moieties are necessary to achieve high enantioselectivities. The results indicated that varying the *ortho* and *para* substituents on the biphenyl and binaphthyl moieties also has a great effect on the asymmetric induction. The highest enantioselectivity (ee up to 90% at 20 bar of syngas and 25°C) in the Rh-catalyzed asymmetric hydroformylation of styrene was obtained by using ligands **21a** and **21d**.

The influence of the backbone was studied comparing the results obtained with the ligands **21** and **24** [37–39]. Surprisingly, ligand **24**, which contains a more sterically hindered phenyl group, provided lower enantioselectivity than ligand **21**.

Scheme 4 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands **21**–**25**



A cooperative effect between the different chiral centers of the phosphite ligands **21f–i** and **25f–i** was demonstrated. Initially, van Leeuwen and co-workers studied the cooperative effect between the chiral ligand bridge and the axially chiral binaphthyl phosphite moieties by comparing ligands **21f**, **g** and **25f**, **g**. The hydroformylation results indicated a suitable combination for ligand **21g** (ees up to 86%) [37–39]. Later, Bakos and co-workers found a similar matched–mismatched effect between the chiral ligand bridge and the chiral phosphite moiety of the ligands **21h**, **i** and **25h**, **i** [40]. Interestingly, the hydroformylation results obtained with ligands **21a** and **21d**, which are conformationally flexible and contain axially chiral biphenyl moieties, are similar to those obtained with ligand **21g**. This indicated that diphosphite ligands containing these biphenyl moieties predominantly exist as a single atropoisomer in the hydridorhodium complexes [$RhH(CO)_2$(diphosphite)] when bulky substituents are present in *ortho* positions [37–39]. It is therefore not necessary to use expensive conformationally rigid binaphthyl moieties.

To investigate whether a relationship exists between the solution structures of the [$RhH(CO)_2$(diphosphite)] species and catalytic performance, van Leeuwen and co-workers extensively studied the [$RhH(CO)_2$(diphosphite)] (diphosphite = **21**, **25**) species formed under hydroformylation conditions by high pressure NMR techniques (HP-NMR) [14 and references therein; 18–20]. From these TBP complexes, two isomeric structures are possible, one containing the diphosphite

coordinated in a bis-equatorial (eq–eq) fashion and one in an equatorial–axial (eq–ax) fashion (Scheme 3). The results indicated that the stability and catalytic performance of the [$RhH(CO)_2$(diphosphite)] (diphosphite = **21**, **25**) species strongly depend on the configuration of the pentane-2,4-diol ligand backbone and on the chiral biaryl phosphite moieties. Thus, ligands **21a**, **21d,** and **21g**, which form well-defined stable bis-equatorial (eq–eq) complexes, lead to good enantiomeric excesses. In contrast, ligands **21i** and **25g**, which form mixtures of complexes, lead to low enantioselectivities [37–39, 42]. The ligand **21a** was also evaluated in the Rh-catalyzed asymmetric hydroformylation of allyl cyanide **1b** and vinyl acetate **1c** but low to moderate enantioselectivities (13% and 58%, respectively) were obtained with these substrates [6].

1,3-Diphosphite ligands derived from 1,2-*O*-isopropyliden-*α*-D-xylofuranose (**26**, **29**) and 6-deoxy-1,2-*O*-isopropyliden-*α*-D-glucofuranose (**27**, **28**, **30**, **31**) were successfully applied in the Rh-catalyzed asymmetric hydroformylation of vinyl arenes (Scheme 5) [43–46].

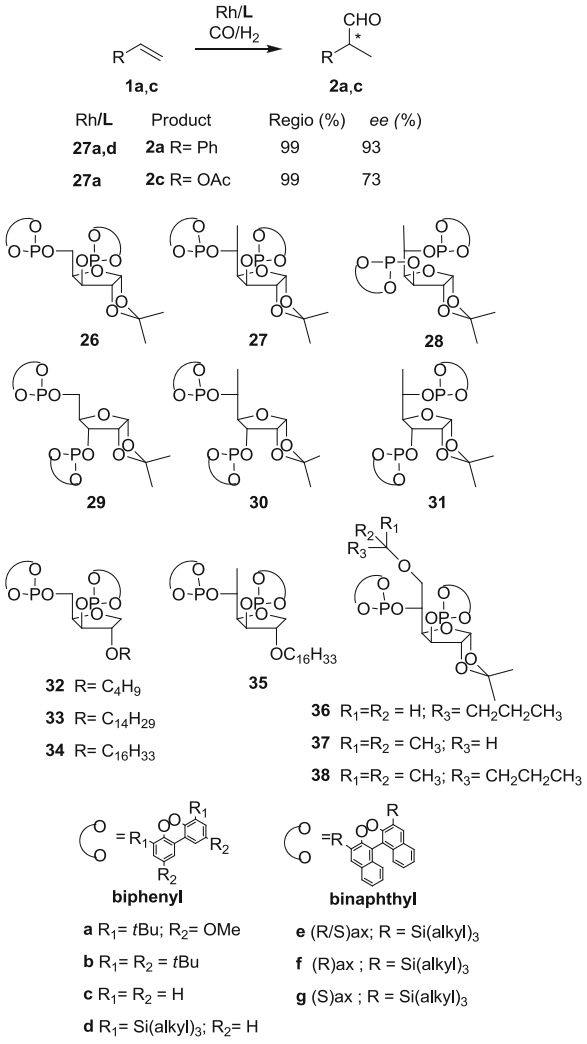
The use of diphosphite ligands **27a**, **d** and **31a**, **d** in the Rh-catalyzed asymmetric hydroformylation of styrene provided the *S*- and *R*-enantiomers of the product with high enantioselectivities (ee up to 93%) and excellent regioselectivity (Scheme 5) [45, 46]. The ligand **27b** was also tested in the hydroformylation of vinyl acetate, obtaining excellent regioselectivity (99%) with an enantioselectivity of 73% [47].

Recently, related C1-symmetry diphosphite ligands conformationally more flexible (**32–35**) or incorporating an increase in steric hindrance at the C-6 position (**36–39**) were synthesized (Scheme 5) [47, 48]. These ligands were probed in the hydroformylation of styrene **1a** and vinyl acetate **1c** with good regio- and enantioselectivity (up to 81% and 68%, respectively), but these selectivities turned out to be lower than with the ligand **27**. Therefore, the bicycle structure and the methyl substituent at C-5 position seem to be required to achieve high enantioselectivity in the hydroformylation of styrene and vinyl acetate when using 1,3-diphosphites derived from carbohydrates.

In summary, the results obtained in the Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes indicate that (1) the absolute configuration of the product is governed by the configuration at the stereogenic centre C-3, (2) the level of enantioselectivity is influenced by the presence of stereocenters at C-3 and C-5 positions, where the phosphorus atoms are attached, (3) bulky substituents in *ortho* positions of the biaryl phosphite moieties are necessary to achieve high levels of enantioselectivity, and (4) pseudo-enantiomer ligands such as **27** and **31** afford the same level of enantioselectivity for both product enantiomers.

Interestingly, the ligands **27** and **31**, for which only [$RhH(CO)_2$(L-L)] species with eq–eq coordination were observed by HP-NMR techniques, provided higher enantioselectivity (ee up to 93%) than the related ligands **28** and **30** (ee up to 64%), for which an equilibrium between the isomeric eq–eq and eq–ax [$RhH(CO)_2$(L)] species was observed by HP-NMR and HP-IR techniques. Therefore, the presence of a single coordination isomer, in this case with ligand coordinated in an

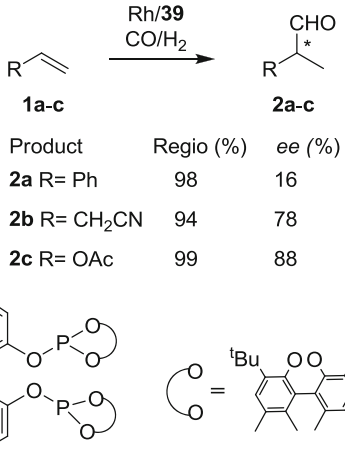
Scheme 5 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands **26–38**



equatorial–equatorial (eq–eq) mode, was observed to produce high levels of enantioselectivity in the Rh-catalyzed asymmetric hydroformylation of styrene, as previously mentioned [45–48].

In contrast with the diphosphites previously mentioned, the KELLIPHITE ligand (**39**), which was developed by Dow Chemical Company, incorporates the chirality in the bisphenol unit, while the backbone is achiral (Scheme 6). The catalytic system containing this ligand afforded very good enantioselectivity in the rhodium-catalyzed hydroformylation of vinyl acetate and allyl cyanide, although low selectivities were obtained in the hydroformylation of styrene [49, 50].

Scheme 6 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligand KELLIPHITE (**39**)



KELLIPHITE (**39**)

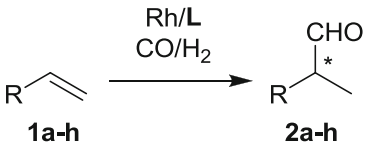
3.2 Phosphine–Phosphite Ligands

The discovery of the (*R*,*S*)-BINAPHOS (**40**) and (*S*,*R*)-BINAPHOS (**41**) ligands in 1993 by Takaya and Nozaki produced a real breakthrough in the Rh-catalyzed asymmetric hydroformylation reaction (Scheme 7) [51].

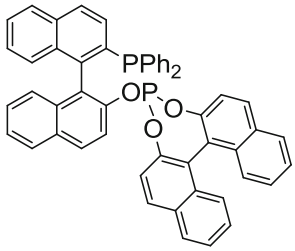
These ligands allowed, for the first time, an increase in the scope of this process since they provided high enantioselectivity in the Rh-catalyzed asymmetric hydroformylation of several classes of monosubstituted alkenes such as vinyl arenes, 1-heteroatom-functionalised alkenes, and disubstituted 1,3-dienes (Scheme 7), and are still currently references in this area [52 and references therein; 53–63]. Excellent regio- and enantioselectivity were achieved with most of these substrates, although the formation of the branched product (21%) was disfavored when but-1-ene was the substrate. In 2003, De Vries and co-workers reported the first Rh-catalyzed asymmetric hydroformylation of allyl cyanide and, although moderate regioselectivity was obtained (72%), the highest enantioselectivity (66%) by far was achieved using the ligand **40** [64]. As a general rule, the presence of electron-withdrawing substituents such as phenyl or heteroatoms in the alkene substrate leads to a control the regioselectivity in favor of the branched product, independently of the ligand used [6].

It is noteworthy that (*R*,*S*)-BINAPHOS (**40**) or the (*S*,*R*)-BINAPHOS (**41**) ligands yield the two enantiomers of the product with high enantioselectivity [65, 66]; however, the (*R*,*R*)- and (*S*,*S*)-BINAPHOS, diastereoisomers of ligands **40** and **41**, yielded much lower enantioselectivity in this process, thus demonstrating the importance of the combination of opposite configurations at the phosphine and phosphite moieties.

In contrast with the previously mentioned diphosphite ligands which coordinate to the Rh centre in an eq–eq fashion, the BINAPHOS ligand was found to coordinate



Product	2a	2b	2c	2d$_1$	2e	2f	2g	2h
R	Ph	CH_2CN	OAc	C_6F_5	CF_3	Et	Phth	S(4-tolyl)
Regio (%)	90	72	86	96	95	21	89	96
ee (%)	94	66	92	98	93	83	85	74



(*R,S*)-BINAPHOS (**40**)

(*S,R*)-BINAPHOS (**41**)

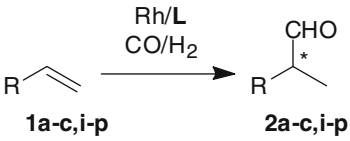
Scheme 7 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using (*R*,*S*)- and (*S*,*R*)-BINAPHOS (**40**) and (**41**)

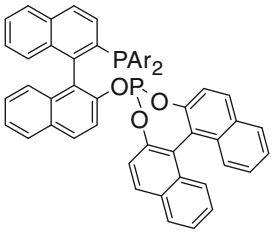
to Rh in an eq–ax mode as a single isomer in the resting state [$RhH(CO)_2$(L–L)] of the process [65, 66].

The second generation of BINAPHOS-type ligands (Scheme 8) was recently developed by the introduction of 3-methoxy substituents on the aryl phosphine units **42** [53, 54], and by replacement of the phosphite group by a phosphoramidite function, yielding the YANPHOS ligand (**43**) (Scheme 8) [67]. The Rh/**42** increased the regio- and enantioselectivity in the asymmetric hydroformylation of styrene, vinylfurans, and thiophenes (Scheme 8).

YANPHOS (**43**) (Scheme 8) provided higher enantioselectivity than the BINAPHOS ligand **40** without altering the regioselectivity in the Rh-catalyzed asymmetric hydroformylation of styrene and vinyl acetate (ee up to 99% and 96%, respectively). Additionally, the ligand **43** provided higher enantioselectivity than KELLIPHITE (**39**) (Scheme 6), although a slight decrease in regioselectivity (80% vs 94%) was observed in the hydroformylation of allyl cyanide (ee up to 96% vs 78%) [68].

Recently, the efficiency of YANPHOS ligand **43** was again demonstrated in the Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with *N*-allyl amides, *N*-allyl phthalamides, and *N*-allyl sulfonamides substituents with excellent

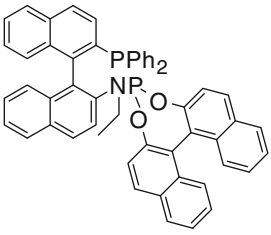




42 Ar = 3-MeOC$_6$H$_4$

Rh/**42**

	Regio(%)	ee(%)
2a R= Ph	95	97
2i R= 2-vinylfuran		79
2j R= 3-vinylfuran		99
2k R= 2-vinylthiophene		93
2l R= 3-vinylthiophene		91



(R,S)-YANPHOS (**43**)

Rh/**43**

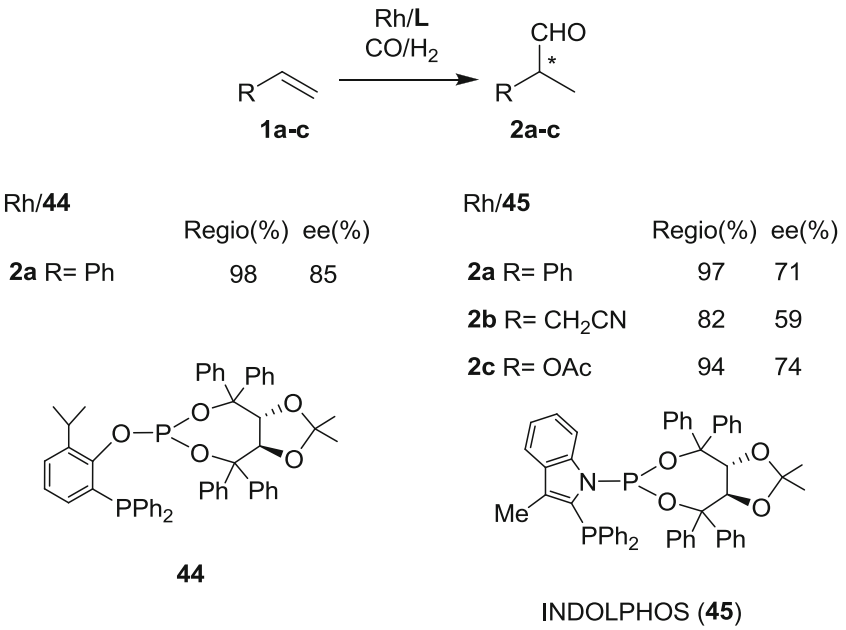
	Regio(%)	ee(%)
2a R= Ph	89	99
2b R= CH_2CN	80	96
2c R= OAc	93	96
2m R= CH_2NHBOC	66	94
2n R= CH_2NHBz	78	95
2o R= $CH_2NHPhthaloyl$	84	96
2p R= CH_2NHSO_2(p-MeOPh)	71	96

Scheme 8 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using the ligands **42** and **43**

ees (up to 96%), good regioselectivities (up to 84%), and a turn over number (TON) up to 9,700.

Inspired by the excellent results obtained using **40** and **41**, several new phosphine–phosphite ligands with different backbones have been developed over the last few years but the catalytic results using these ligands provided lower enantioselectivity (from 20% to 85%) than those previously achieved with the original BINAPHOS ligand [69–74]. Some of these ligands help to elucidate the correlation between the ee and the electron-withdrawing properties of the substitution in the alkene [75].

Based on the BINAPHOS structure, a new family of phosphine–phosphite and phosphine–phosphoramidite ligands was constituted using a Taddol-based backbone in the phosphite or phosphoramidite moiety, respectively (Scheme 9) [76, 77]. These ligands were applied in the Rh-catalyzed asymmetric hydroformylation of



Scheme 9 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using Taddol-based ligands (**44** and **45**)

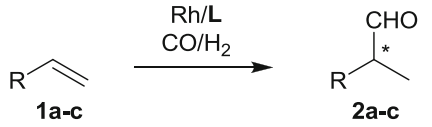
styrene, allyl cyanide, and vinyl acetate with excellent regioselectivities (up to 98%) and good ees (up to 85%).

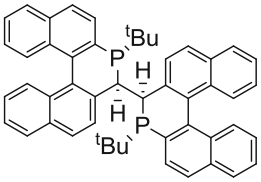
3.3 Bisphospholane Ligands

Several bisphospholane chiral ligands known as efficient ligands for asymmetric hydrogenation were recently evaluated in asymmetric hydroformylation (Scheme 10) [78].

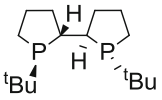
Two ligands, namely (*S*)-BINAPINE (**46**) and (*S*,*S*,*R*,*R*)-TANGPHOS (**47**), were found to give excellent enantioselectivities in the asymmetric hydroformylation of styrene, allyl cyanide, and vinyl acetate (Scheme 10) [79]. It is noteworthy that the enantioselectivities achieved for product **2b** with these ligands are the highest ever reported for the allyl cyanide substrate.

The discovery of the biphospholane scaffold as a new privileged structure for asymmetric alkene hydroformylation has triggered new research efforts for novel and improved bisphospholane-type ligands. In this context, the (*R*,*R*)-Ph-BPE ligand (**48**) (Scheme 10), derivative of DuPhos, was identified as an outstanding ligand for asymmetric hydroformylation since excellent regio- and enantioselectivities were achieved for styrene, allyl cyanide, and vinyl acetate as substrates with

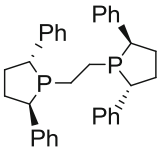




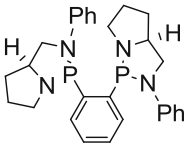
(R,S)-BINAPINE (**46**)



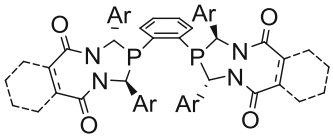
(S,S,R,R)-TANGPHOS (**47**)



(R,R)-Ph-BPE (**48**)



Esphos (**49**)



Bis-3,4-diazaphospholane (**50**)

Product	**2a**		**2b**		**2c**	
Rh/**L**	R= Ph		R= CH_2CN		R= OAc	
			Regio (%)	ee(%)		
46	90	94	87	94	97	87
47	93	90	88	93	97	83
48	98	94	88	90	99	82
49					94	89
50	97	89	83	87	98	96

Scheme 10 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using the diphosphine ligands **46**–**50**

this ligand [80]. Several spacers between the two phosphorus donor atoms were evaluated and the two-carbon bridge of **48** provided the highest selectivity for all three substrates [79].

A series of bis-2,5-diazaphospholane ligands was also probed in this process and the ESPHOS (**49**) proved to be optimal, with the best results being obtained in the hydroformylation of vinyl acetate (ee up to 89%) (Scheme 10) [81]. The bis-3,4-diazaphospholane ligand **50** also provided excellent regio- and enantioselectivity (ee up to 96%) in this reaction (Scheme 10) [82].

3.4 Bis-Phosphonite Ligands

The bis-phosphonite ligand **51** provided moderate selectivities in the hydroformylation of styrene and allyl cyanide (Scheme 11). However, this ligand provided an excellent 91% ee in the hydroformylation of vinyl acetate [83]. The related diphosphinite ligand derived from ferrocene **52** was also recently reported by Ding and co-workers and its application in the Rh-catalyzed asymmetric hydroformylation of styrene and vinyl acetate provided good conversion but lower enantioselectivities in the hydroformylation of styrene and vinyl acetate (up to 55% and 83%, respectively) [84].

3.5 Phosphite–Phospholane Ligands

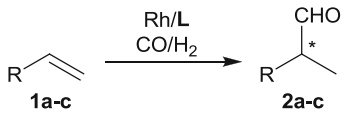
Very recently it was demonstrated that branched aldehydes can be produced by hydroformylation of terminal alkenes of formula $RCH_2CH{=}CH_2$ using a new hybrid ligand called "bobphos" (**53**) (Scheme 12) [85]. This ligand, result of the combination of KELLIPHITE and Ph-bpe, provided good to excellent conversions (between 64% and 99%), very good regioselectivities (between 71% and 91%), and excellent ees (up to 93%) for a series of terminal alkenes (Scheme 12).

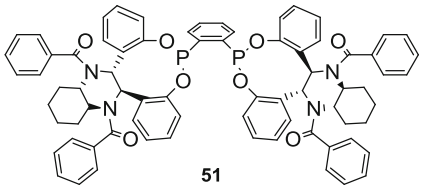
3.6 Monodentate Phosphorus-Based Ligands

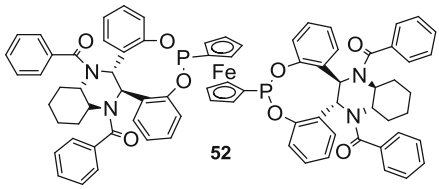
Nowadays, despite the successful use of monodentate ligands in many transition metal catalyzed processes, there are only a few reports concerning their use in asymmetric hydroformylation. Achieving high enantioselectivities in this process using those ligands remains a challenge.

Although the use of monodentate phosphorus donor ligands usually provides higher catalytic activity than their bidentate counterparts, only moderate to good enantioselectivities have been reported in asymmetric hydroformylation processes so far. For instance, the ligand **57** was tested in the Rh-catalyzed asymmetric hydroformylation of styrene and allyl cyanide and provided moderate enantioselectivities (Scheme 13). When vinyl acetate was the substrate, very poor ees were obtained (Scheme 13) [49, 50]. However, in 2004, Ojima and co-workers reported the use of the phosphoramidite ligand **55** (Scheme 13), related to monophosphite **54**, in the Rh-catalyzed asymmetric hydroformylation of allyl cyanide and achieved excellent regioselectivities together with the highest enantiomeric excess (80%) ever reported for this reaction with a monodentate ligand [86]. These results, although still far from those obtained with bidentate ligands, clearly indicated that achieving high ees using monodentate ligands is possible.

Scheme 11 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with ligands **51** and **52**







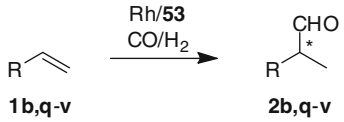
Product	2a		2b		2c	
Rh/**L**	R= Ph		R= CH_2CN		R= OAc	
			Regio (%)	*ee*(%)		
51	92	79	82	79	98	91
52	95	55			94	83

In 2005, Breit report an alternative approach to the classical synthesis of bidentate ligands for hydroformylation by using the self-assembly of bidentate ligands based on an A-T base-pair model [87]. This method presents the advantage of allowing the rapid screening of various pairs of available monodentate ligands to obtain the most suitable combination for each substrate, overcoming the typical synthetic limitations for new bidentate ligands. Later, van Leeuwen and Reek reported the template-induced formation of chelating heterobidentate ligands by the self-assembly of two distinct monodentate ligands on a rigid bis-zinc(II)-salphen template with two identical binding sites (Scheme 14) [88, 89]. The templated heterobidentate ligand **56** induced much higher enantioselectivities (ee up to 72%) than any of the corresponding homobidentate ligands or non-templated mixed ligand combinations (ee up to 13%) in the Rh-catalyzed asymmetric hydroformylation of styrene.

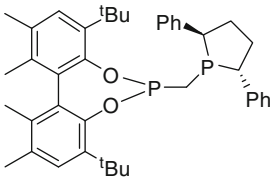
4 Rh-Catalyzed Asymmetric Hydroformylation of Disubstituted Alkenes

The Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes has received much less attention than that of their monosubstituted counterparts. To the best of our knowledge, only a few examples of asymmetric Rh-catalyzed hydroformylation of

Scheme 12 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes with ligand **53**



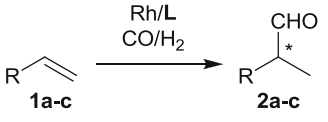
1b,q-v **2b,q-v**



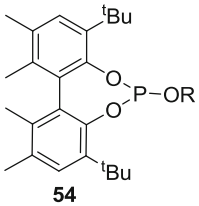
bobphos (**53**)

Product	Regio (%)	*ee* (%)
2b R= CH_2CN	91	81
2q R= Bz	80	90
2r R= $CH_2C_6F_5$	86	91
2s R= CH_2(*p*-^{t}BuPh)	75	92
2t R= CH_2CH_2Ph	71	75
2u R= Bu	75	93
2v R= $CH_2CON(Ph)(CH_3)$	81	92

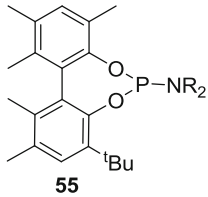
Scheme 13 Rh-catalyzed asymmetric hydroformylation of monosubstituted alkenes using ligands **54** and **55**



1a-c **2a-c**



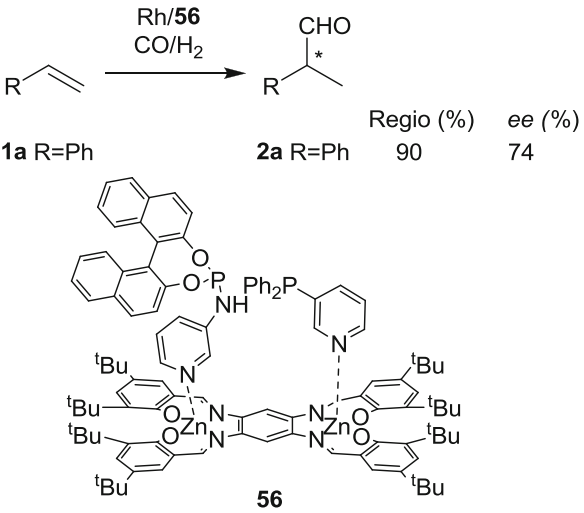
54



55

Product	**2a**	**2b**	**2c**
Rh/**L**	R= Ph	R= CH_2CN	R= OAc
		Regio (%) *ee*(%)	
54	94 38	84 43	93 8
55		96 80	

Scheme 14 Rh-catalyzed asymmetric hydroformylation of styrene using the templated ligand **56**



1,2-disubstituted and 1,1-disubstituted alkenes have been reported so far (Scheme 1) [25, 47, 90–110].

4.1 Linear 1,2-Disubstituted Alkenes

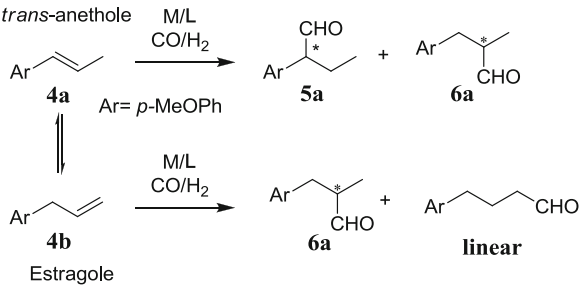
The asymmetric hydroformylation of propenylbenzenes was originally studied by Kollár using $PtCl_2$(bdpp)/$SnCl_2$ as catalyst [90]. The reaction was performed using *trans*-anethole and estragole as substrate in order to synthesize the branched chiral aldehydes **5a** and **6a** (Scheme 15). However, the formation of the linear aldehyde was observed due to *trans*-anethole isomerization into terminal monosubstituted estragole. Furthermore, moderate to low enantioselectivities were obtained (ee up to 27%). The 1,3-diphosphite ligand **26** was used in the Rh-catalyzed asymmetric hydroformylation of *trans*-anethole **4a** and estragole **4b** (Scheme 15) but moderate to low enantioselectivities were achieved (ee up to 15%) [91].

Nozaki et al. reported the asymmetric Rh-catalyzed hydroformylation of *trans*-anethole **4a** into **5a** using the BINAPHOS ligand **40** with excellent regioselectivity (98%) and a remarkable 80% ee [92, 93].

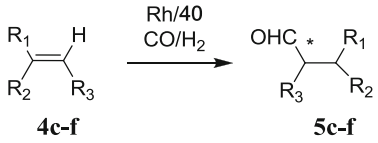
In the Rh-catalyzed asymmetric hydroformylation of 1,2-alkyl-disubstituted alkenes (Scheme 16) as substrates, the BINAPHOS ligand **40** provided the highest ee values [92, 93]. Interestingly, it was reported that the *E*-isomers **4d** and **4f** yielded lower enantioselectivity than their *Z*-counterparts **4c** and **4e**.

A monodentate phosphoramidite template ligand was developed by Reek et al. and used in the asymmetric Rh-catalyzed hydroformylation of *E*-2-octene (**5i**) (Scheme 17). This ligand (**57**) exhibits a supramolecular control over the Rh center, due to the presence of two pyridine functions in the bis(naphthol) skeleton that are

Scheme 15 Isomerization processes and asymmetric hydroformylation of *trans*-anethole and estragole



Scheme 16 Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes



Product	*ee* (%)
5c R_1= H, R_2=R_3= Me	85
5d R_1= Me, R_2= H, R_3= Me	48
5e R_1= H, R_2=R_3= Et	79
5f R_1= Et, R_2= H, R_3= Et	69

bound to zinc(II) porphyrins. With this ligand, useful conversions (up to 56%) with moderate ees (up to 45%) were achieved. When the BINAPHOS ligand **40** was used in the same reaction, similar conversion (55%) was obtained although without significant enantioselective induction [94].

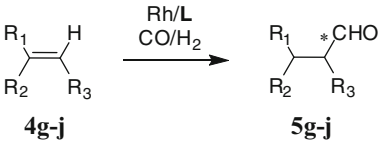
Very recently the same author described the use of this ligand (**57**) in the asymmetric Rh-catalyzed hydroformylation of internal alkenes like *E*-2-hexene (**4g**), *E*-2-heptene (**4h**), and *E*-2-nonene (**4j**), achieving conversions up to 65% and moderate ees (up to 47%) [95].

The same research group formerly reported the use of encapsulated catalysts for the selective hydroformylation of unfunctionalized alkenes [96]. The ligand (**58**) (Scheme 18) acts as a supramolecular "box" with the bis-[Zn(salphen)] moiety as a template and two chiral phosphoramidite ligands as the pillars. In the asymmetric Rh-catalyzed hydroformylation of internal alkenes, the inner aldehydes with *R* configuration were preferably formed (with the exception of 3-hexene for which the *S*-aldehyde was produced).

4.2 Monocyclic 1,2-Disubstituted Alkenes

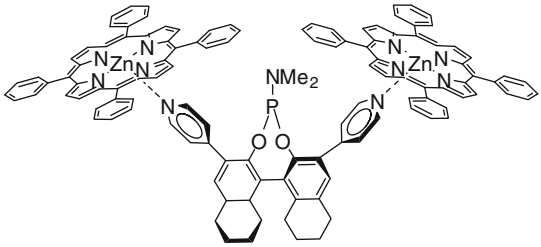
Among monocyclic 1,2-disubstituted alkene substrates, five-membered ring heterocycles such as dihydrofurans and dihydropyrroles have been the most studied.

Scheme 17 Rh-catalyzed asymmetric hydroformylation of disubstituted alkenes with ligands (**40**) and (**57**)



4g-j **5g-j**

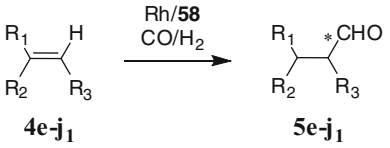
Product		
	5g	R_1= Me, R_2=H, R_3= Pr
	5h	R_1= Me, R_2=H, R_3= Bu
	5i	R_1= Me, R_2=H, R_3= Pent
	5j	R_1= Me, R_2=H, R_3= Hex



57

Rh/**40**	Conv (%)	*ee*(%)	Rh/**57**	Conv (%)	*ee*(%)
			5g	65	46
			5h	43	44
5i	55	0	**5i**	56	45
			5j	52	47

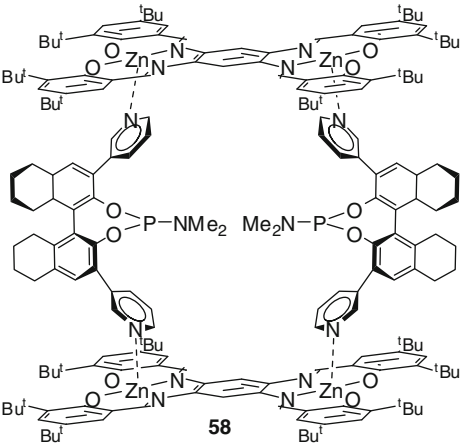
With these substrates, the simultaneous control of the chemo-, regio-, and enantioselectivity is a key issue since the presence of a heteroatom in the cycle favors in some cases an isomerization process in the presence of a metal-hydride species. Previous studies using achiral ligands demonstrated that the reaction conditions greatly affected the chemo- and regioselectivity of this reaction [97, 98]. Indeed, allyl ethers were shown to isomerize rapidly into their vinyl analogues under hydroformylation conditions (Scheme 19). This isomerization process is of critical importance since it has a direct influence on the regioselectivity of the reaction, but also on the enantioselectivity since the opposite enantiomers of tetrahydro-3-carbaldehyde are formed from the allylic **4k–m** and vinylic **4n–p** isomers of the substrate [99]. It is therefore required to limit the isomerization in order to obtain high selectivities. In the Rh-catalyzed asymmetric hydroformylation of 2,5-dihydrofuran **4k**, Nozaki et al. reported the first successful results using the BINAPHOS ligand **40** which yielded total regioselectivity to the tetrahydro-3-carbaldehyde **5k** with 68% ee (*R*) (Scheme 21) [92, 93, 100]. However, when the 2,3-dihydrofuran **4n** was tested with the same catalyst, no regioselectivity was observed and the ee obtained for the



4e-j$_1$ **5e-j$_1$**

Product

5e	R_1= H, R_2=Et, R_3= Et	**5i**	R_1= Me, R_2=H, R_3= Pent
5f	R_1= Et, R_2= H, R_3= Et	**5i$_1$**	R_1= H, R_2=Me, R_3= Pent
5h	R_1= Me, R_2=H, R_3= Bu	**5j**	R_1= Me, R_2=H, R_3= Hex
5h$_1$	R_1= H, R_2=Me, R_3= Bu	**5j$_1$**	R_1= H, R_2=Me, R_3= Hex



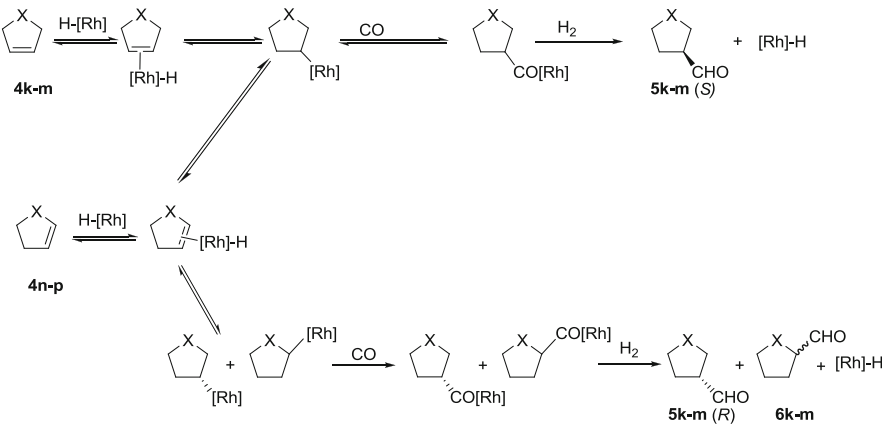
58

Rh/**58**	Conv(%)	Inner(%)	*ee*(%)		Conv(%)	Inner(%)	*ee*(%)
5e	11	na	78 (S)	**5i**	10	60	86 (R)
5f	19	na	81 (S)	**5i$_1$**	20	70	93 (R)
5h	9	55	83 (R)	**5j**	13	52	81 (R)
5h$_1$	24	67	91 (R)	**5j$_1$**	26	61	90 (R)

Scheme 18 Rh-catalyzed asymmetric hydroformylation of internal alkenes with the ligand **58**

aldehyde **5k** decreased to 38% with *S* configuration. This catalytic system was thus suitable to avoid isomerization of **4k** into **4n** but not selective for the hydroformylation of **4n**. In the same study, the amine analogues **4l**, **4m,** and **4o** were also tested as substrates using the same catalytic system (Scheme 19) and similar results were obtained.

The previously mentioned 1,3-diphosphites **27**–**38** derived from carbohydrates were successfully applied in the Rh-catalyzed hydroformylation of these substrates [47, 101, 102]. The results indicated that ligands **27**, **35**–**38**, which have a glucose



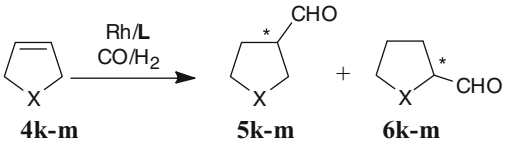
Scheme 19 Isomerization processes observed during the Rh-asymmetric hydroformylation of five-membered heterocyclic alkenes

configuration, are the most appropriate to obtain high enantioselective induction in the hydroformylation of these substrates. In the case of the 2,5-dihydrofuran **4k**, the highest enantioselectivity in the aldehyde **5k** was obtained using ligand **35b** (88% *S*). Using this ligand, no isomerization was observed under hydroformylation conditions. Interestingly, the presence of bulky substituents at C-5, such as in ligands **36b**–**38b**, was shown to increase the degree of isomerization. When the 2,3-dihydrofuran (**4n**) was used as substrate, ees up to 84% (*R*) in aldehyde **5k** were achieved using ligands **36b**–**37b**, together with a regioselectivity of 80%. The 2,5-dihydropyrrole **4l** was also tested with the Rh/**27b** system, achieving comparable results to those previously reported using ligand **40** (71% and 66%, respectively).

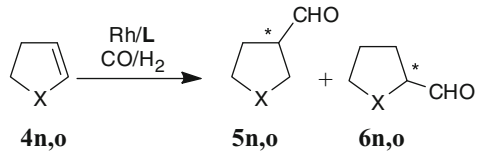
Formerly, Reek and co-workers described the synthesis and application of the ligand **59** in the Rh-catalyzed asymmetric hydroformylation of the cyclic olefins **4k**–**o** (Scheme 20). This system provided regioselectivities up to 99% and excellent ees (up to 91%). It should be noted that the highest enantioselectivities (91%) reported to date for the substrates **4k** and **4n** were achieved with this ligand [96, 103].

Interestingly, in the Rh-catalyzed asymmetric hydroformylation of the cyclic alkene **4n** (Scheme 20), which usually selectively produces the aldehyde **5n**, high regioselectivity (68%) to the aldehyde **6n** was recently reported, together with good ees (62%) using the ligand **60** (the highest reported to date) [96].

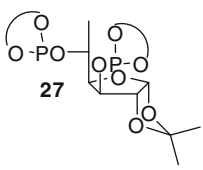
The asymmetric Rh-catalyzed hydroformylation of dioxapines **4q**, **r** was reported using the BINAPHOS ligand **40** and 1,3-diphosphite ligands derived from carbohydrates **61b** (Scheme 21) [92–100, 102]. Using the ligand **40**, total regioselectivity to **5q**, **r** was achieved, together with ees up to 76%. Among the carbohydrate derived ligands that were tested, the ligand **61b** provided the best results (Scheme 21), affording total regioselectivity to **5q**, **r** and up to 68% ee, thus indicating that no isomerization of **4q**, **r** had occurred.

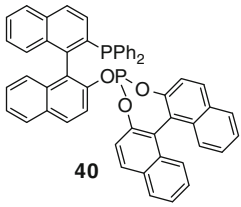


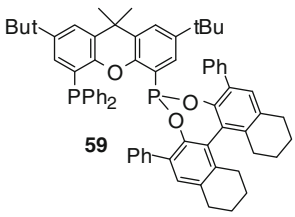
Product	5k		5l		5m	
Rh/L	X=O		X=NBoc		X=NAc	
	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)
27b	99	75 (*S*)			99	71 (-)
35b	99	88 (S)				
40	99	68 (*R*)	99	73 (*R*)	99	66 (+)
59	99	91 (*S*)	90	86 (+)	99	85

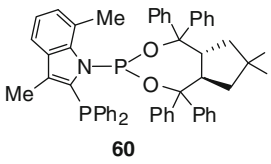


Product	5n		5o		6n	
Rh/L	X=O		X=NBoc		X=O	
	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)	Regio (%)	*ee*(%)
27b	76	75 (*R*)				
36b	78	83 (*R*)				
37b	78	84 (*R*)				
40	50	38 (*S*)	33	71 (*S*)		
59	80	91 (*R*)				
60	32	73 (*R*)			68	62 (*R*)





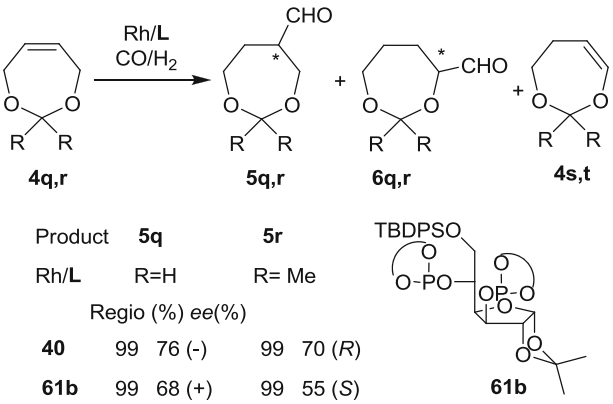




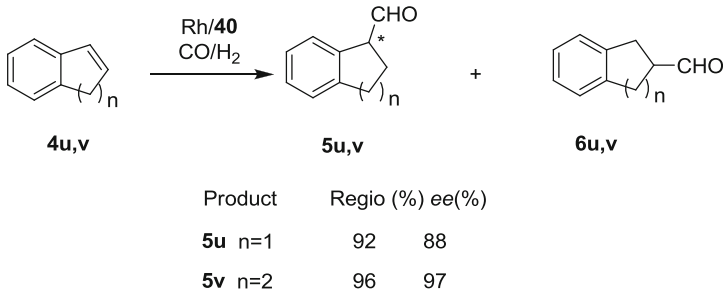
Scheme 20 Rh-catalyzed asymmetric hydroformylation of five-membered heterocyclic alkenes **4k–o**

4.3 Bicyclic 1,2-Disubstituted Alkenes

The Rh-catalyzed asymmetric hydroformylation of substrates **4u** and **4v** was reported by Nozaki et al. using the ligand **40** (Scheme 22) [92, 93]. The results are really remarkable, in particular with substrate **4v**, for which compound **5v** was obtained with practically total regio and enantioselectivity (Scheme 22). The corresponding products **5u** and **5v** are of interest since the aldehyde **5u** can be converted in a single step into the corresponding amine which exhibits hypotensive activity and the product **5v** is a synthetic intermediate to produce a vasoconstrictor tetrahydrozoline [104].



Scheme 21 Rh-catalyzed asymmetric hydroformylation of **4q**, **r**

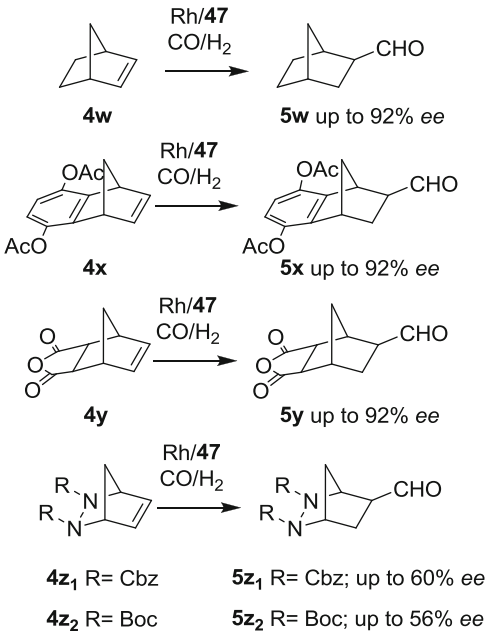


Scheme 22 Rh-catalyzed asymmetric hydroformylation of bicyclic alkenes using (*R*,*S*)-BINAPHOS ligand **40**

Another bicyclic alkene substrate of interest for carbonylation reactions is the norbornene **4w** and its derivatives. The first reports on the asymmetric Rh-catalyzed hydroformylation of norbornene afforded low enantiomeric induction with ees below 25% [105, 106]. In 2005, Bunel and co-workers reported the first highly enantioselective Rh-catalyzed hydroformylation of norbornene into the *exo* aldehyde with ees up to 92% using the diphospholane ligands **47** and **48** [107]. Using these ligands, they also reported the hydroformylation of several derivatives of this substrate with similar enantioselectivities (Scheme 23).

Recently, the hemispherical diphosphite ligands **62** (Fig. 1) with a conical calixarene skeleton was used in the asymmetric Rh-catalyzed hydroformylation of norbornene, achieving enantioselectivities up to 61% with the *exo* aldehyde being the major product [108].

More recently, the KELLIPHITE ligand (**39**) was employed in the Rh-catalyzed asymmetric hydroformylation of the bicyclic lactam azababicyclo-[2.2.1]hept-



Scheme 23 Rh-catalyzed asymmetric hydroformylation of norbornene derivatives using the diphospholane ligand **47**

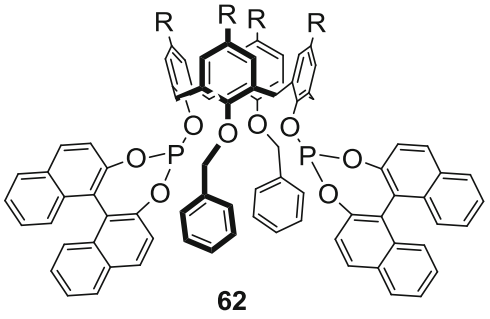
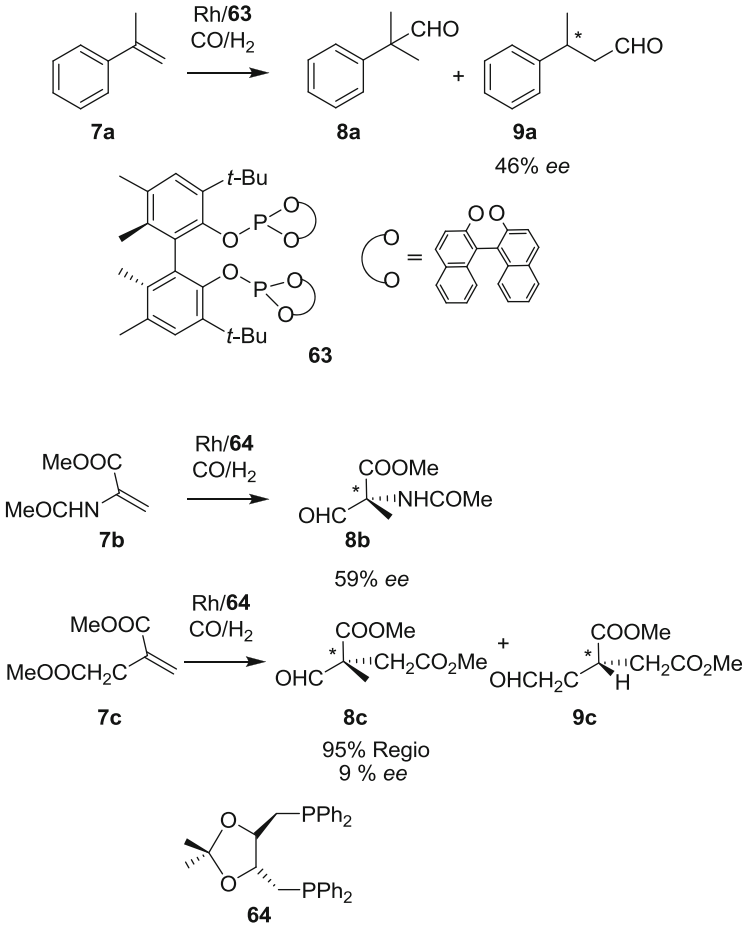


Fig. 1 Hemispherical diphosphite ligands **62** with a conical calixarene skeleton

5-en-3-one with very good results. The reaction was completely *exo*-selective, yielding total conversions and excellent regioselectivities (up to 91%) [109].

4.4 1,1′-Disubstituted Alkenes

The asymmetric hydroformylation of 1,1′-disubstituted alkenes differs from the classical asymmetric hydroformylation of monosubstituted terminal alkenes since the desired product is the linear aldehyde (Scheme 1).

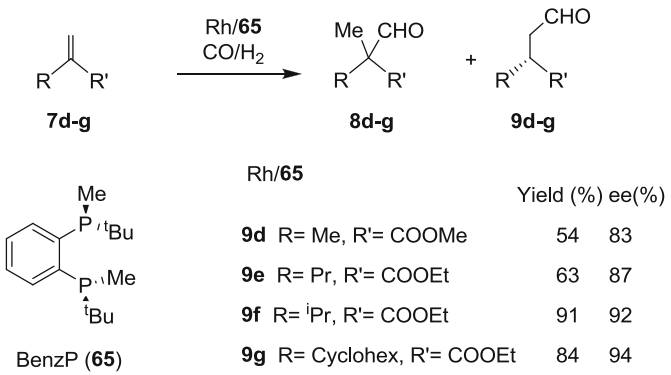


Scheme 24 Rh-catalyzed asymmetric hydroformylation of 1,1′-disubstituted alkenes

Indeed, the Rh-catalyzed asymmetric hydroformylation of 1,1-methyl styrene (**7a**) using diphosphite ligand **63** (Scheme 24) to form the linear product **9a** was recently patented. The enantioselectivity was, however, moderate (ee up to 46%) [110].

Interestingly, however, when dehydro amino acid derivatives **7b** and dimethyl itaconate **7c** were used as substrates (Scheme 24) in the presence of [RhH(CO)$(PPh_3)_3$] and 1–6 equiv. of the (*R*,*R*)-DIOP ligand **64**, the formation of the branched products was largely favored with moderate enantioselectivity (ees up to 59%). In this process highly functionalized quaternary carbons are easily obtained from common products. This interesting reaction deserves more attention by researchers in the field. It should be noted that when the α,β-unsaturated carboxylic compounds such as **7c** are hydroformylated in the presence of the [$PtCl(SnCl_3)$], the only hydroformylation product obtained was the linear aldehyde with ees up to 82% [25].

Very recently, Buchwald et al. reported the Rh-catalyzed asymmetric hydroformylation of 1,1-disubstituted alkenes (α-alkyl acrylates) using the 1,3-diphosphine



Scheme 25 Rh-catalyzed asymmetric hydroformylation of α-alkyl acrylates

ligand BenzP (**65**). With this ligand, good regio- (up to 91%) and enantioselectivities (up to 94%) were achieved (Scheme 25) [111]. The fine tuning of the partial pressures of CO/H_2 minimizes the problem of the side reactions; in fact, the mild reaction conditions make it safe for general laboratory use (10 bar 1:5 CO/H_2, 100°C).

4.5 Other Substrates

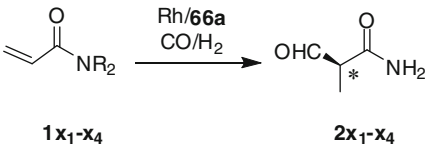
In this section, recent reports on the Rh-catalyzed asymmetric hydroformylation of "non common" alkene substrates using chiral phosphorus donor ligands and scaffolding [112] ligands (metal-organic cooperative catalysts) are presented.

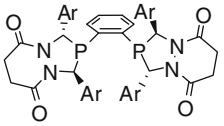
4.5.1 α,β-Unsaturated Amides, 1,3-Dienes, *N*-Vinyl Carboxamides, Allyl Carbamates, and Allyl Ethers

The substrate scope for the hydroformylation of dialkyl acrylamides $\mathbf{1x_{1-4}}$ has so far been limited to methacrylamide, acrylamide or *N*-benzyl acrylamide, with low enantioselective induction (20–50% ees) [113, 114].

However, the use of a bis-diazaphospholane ligand (**66a**) in the Rh-catalyzed asymmetric hydroformylation of *N*,*N*-dialkyl acrylamides was recently described, achieving nearly total regioselectivity and ees up to 82% (Scheme 26) [115].

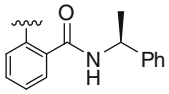
The use of the bis-3,4-diazaphospholane type ligands (**66**) has also been reported in the rhodium catalyzed hydroformylation of several 1,3-diene substrates (1,3-dienes, *N*-vinyl carboxamides, allyl carbamates, and allyl ethers) with excellent regio- and enantioselectivities by Landis et al. [116, 117]. Total conversions with good regioselectivities (>88%) and excellent enantioselectivities (91–97%) were achieved (Scheme 27).





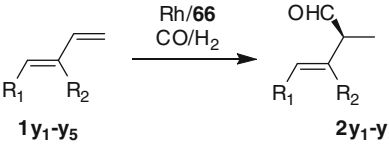
Bis-3,4-diazaphospholane (**66a**)

Ar=

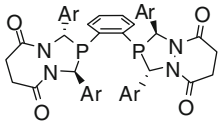


Rh/**66a**		Regio (%)	ee(%)
2x$_1$	R= Me	98	68
2x$_2$	R= Et	97	82
2x$_3$	R= *i*-Pr	98	74
2x$_4$	NR_2=NMe(OMe)	98	71

Scheme 26 Rh-catalyzed asymmetric hydroformylation of *N*,*N*-dialkyl acrylamides

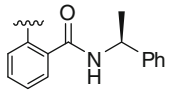


1y$_1$-y$_5$ **2y$_1$-y$_5$**

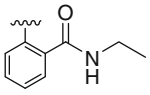


Bis-3,4-diazaphospholane

66a (S,S) Ar=



66b (S) Ar=

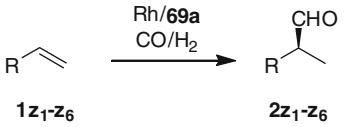


Rh/**66a**		Regio (%)	ee(%)
1y$_1$	R_1= Ph, R_2= H	99	91
1y$_2$	R_1= 2-furan, R_2= H	99	97
1y$_3$	R_1= MeO, R_2= H	99	94

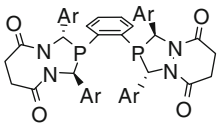
Rh/**66b**		Regio (%)	ee(%)
1y$_4$	R_1= Ph, R_2= Me	88	93
1y$_5$	R_1= 2-furan, R_2= Me	98	93

Scheme 27 Rh-catalyzed asymmetric hydroformylation of 1,3-dienes with ligands **66a** and **66b**

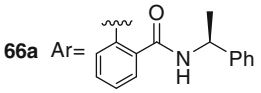
The ligand **66a** was also successfully employed in the Rh-catalyzed asymmetric hydroformylation of other alkene substrates containing amide (**1z$_1$**–**z$_3$**) and ether (**1z$_4$**–**1z$_6$**) substituents, with ees up to 99% and 82%, respectively (Schemes 26 and 28) [117].



1z$_1$-z$_6$ **2z$_1$-z$_6$**



Bis-3,4-diazaphospholane



Rh/**66a**		Regio (%)	ee(%)
2z$_1$	R= NHCOOBn	99	94
2z$_2$	R= NHCOO^{t}Bu	97	99
2z$_3$	R= $NHCOCF_3$	98	99
2z$_4$	R= CH_2OTMS	67	97
2z$_5$	R= CH_2OPh	72	96
2z$_6$	R= $CH(OAc)_2$	82	93

Scheme 28 Rh-catalyzed asymmetric hydroformylation of monosubstituted enamides and other allylic substrates with the ligand **66a**

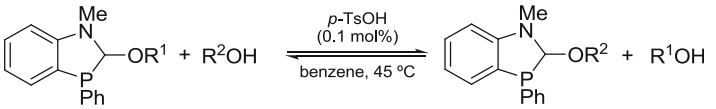
4.5.2 Scaffolding Ligands

The term "catalyst-directing groups" was defined for organocatalysts that are able to form simultaneously covalent bonds with a substrate and dative bonds with a metal catalyst, which allow them to direct metal-catalyzed transformations [118]. In general, these "scaffolding ligands" were named by analogy with scaffolding proteins, which promote biological processes [119].

Using such methodology, the groups of Tan and Breit reported the highly regioselective Rh-catalyzed hydroformylation of homoallylic alcohols [118, 120]. Tan et al. designed the alkoxy benzoazaphosphole ligand **67** derived from *N*-methyl aniline that undergoes facile exchange with other alcohols or secondary amines (Scheme 29) [120].

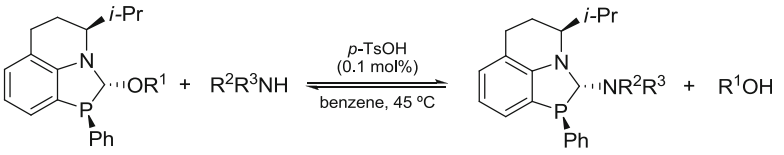
The asymmetric hydroformylation of several alkene substrates was performed by Tan and co-workers using scaffolding ligands containing a tetrahydroisoquinoline group on the alkoxy benzoazaphosphole yielding the scaffolding ligand **69** (Scheme 30).

The Breit research group demonstrated that Ph_2POMe was a suitable catalytic directing group for hydroformylation [118]. Notably, the functionalization of 1,2-disubstituted olefins and other substrates containing stereocenters proceeded with excellent regio- and stereo- selectivity. Additionally, the chemoselective hydroformylation of homoallylic alcohols over unactivated alkenes was observed.



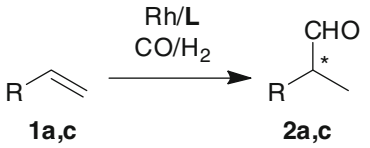
67 68

Scheme 29 Alkoxy benzoazaphosphole catalytic directing group



69 70

Scheme 30 Tetrahydroisoquinoline alkoxy benzoazaphosphole scaffolding ligand

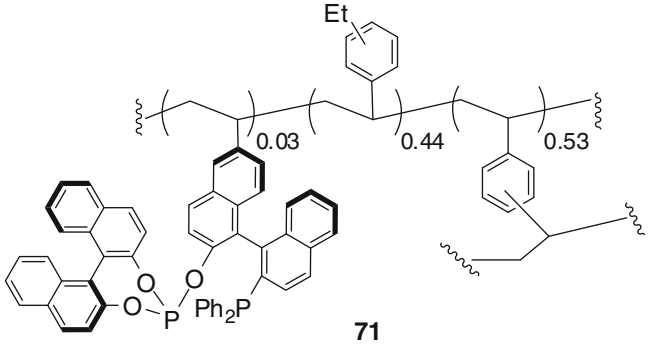


1a,c 2a,c

Product

2a R=Ph

2c R=OAc

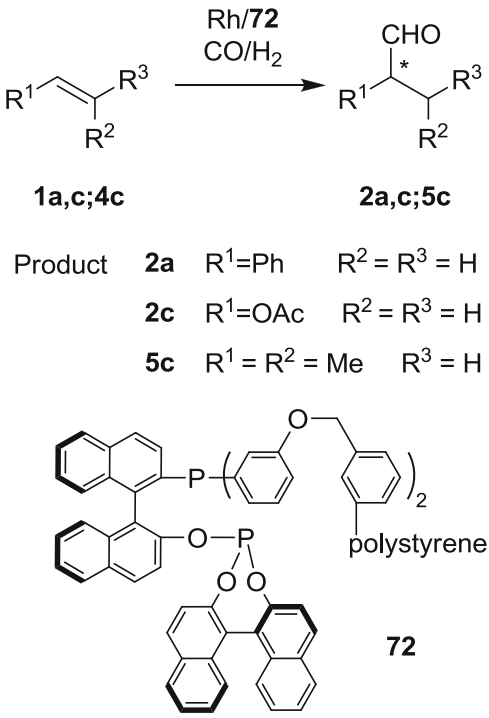


71

Rh/**40**	Regio(%)	*ee*(%)	Rh/**71**	Regio(%)	*ee*(%)
2a	89	92	**2a**	85	90
2c	84	92	**2c**	90	93

Scheme 31 Rh-catalyzed asymmetric hydroformylation of styrene and vinylacetate catalyzed with the ligand (*R*,*S*)-BINAPHOS (**40**) and the polystyrene supported ligand (**71**)

Scheme 32 Rh-catalyzed asymmetric hydroformylation with the polystyrene supported ligand (*R*,*S*)-BINAPHOS (**72**)



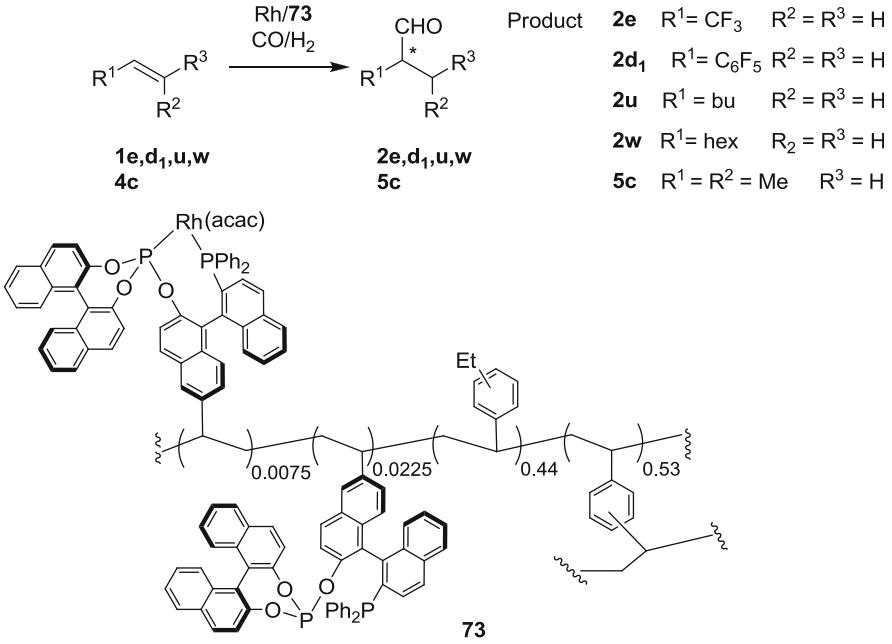
Rh/**72**	Regio(%)	*ee*(%)	TOF(h^{-1})
2a	89	92	
2b	87	92	
5c		80	27

5 Heterogenized Catalytic Systems for Asymmetric Hydroformylation of Alkenes

The development of supported chiral catalysts to facilitate its separation from the products and its recycling or its integration into continuous flow systems, is still a challenge in the field of asymmetric catalysis.

In the field of asymmetric hydroformylation, most of the results with heterogenized catalytic systems were reported by the group of Nozaki et al. using BINAPHOS derived systems.

In the late 1990s, the (*R*,*S*)-BINAPHOS ligand (**71**) was immobilized by covalent bonding to a high cross-linked polystyrene and studied the Rh-catalyzed asymmetric hydroformylation of styrene and vinyl acetate [121]. This catalytic system provided



Rh/**73**	Regio(%)	*ee*(%)	TOF(h^{-1})
2e	95	90	9
2d$_1$	89	88	
2u	21	60	
2w	21	73	
5c		82	10

Scheme 33 Rh-catalyzed asymmetric hydroformylation with the polystyrene supported catalyst **73**

good conversions (up to 83%), excellent regioselectivities (up to 90%), and ees up to 93% (Scheme 31).

A few years later, the new class of polymer-supported (*R*,*S*)-BINAPHOS (**72**) was reported in the asymmetric hydroformylation of styrene and vinyl acetate under batch conditions and in the transformation of *Z*-2-butene under continuous-flow conditions [57]. The results obtained in the hydroformylation of styrene and vinyl acetate were similar to those previously reported, but the most remarkable results were achieved in the continuous-flow asymmetric hydroformylation of *Z*-2-butene for which a TOF value of 27 h^{-1} and ee of 80% were obtained (Scheme 32).

In 2003, the use of the (*R*,*S*)-BINAPHOS-Rh(I) catalyst (**73**) (Scheme 33), which is covalently anchored to a highly cross-linked polystyrene support, was reported in the asymmetric hydroformylation of several alkenes in the absence of organic solvents [55]. In the hydroformylation of *Z*-2-butene this system provided total regioselectivity with ees up to 82%. The heterogenized catalysts were also employed

Table 1 Sequential conversion of various olefins using a continuous $scCO_2$ flow system

Cycle	Olefin	Conversion (%)	*b*/*l*	ee (%)
1	**1a**	49	82/18	77
2	**1c**	5	70/30	74
3	**1w**	47	21/79	73
4	**1u**	40	21/79	60
5	**1a**	36	81/19	82
6	$\mathbf{1d_1}$	27	89/11	88
7	$\mathbf{1d_2}$	21	91/9	78
8	**1a**	54	80/20	80

in a continuous vapor-flow column reactor to transform 3,3,3-trifluoropropene to the corresponding branched aldehyde with regioselectivity up to 95% and ee of 90%. Less volatile olefins such as 1-hexene, 1-octene, and pentafluoro styrene were successfully converted into the corresponding branched aldehydes with high ee through a flow column reactor with supercritical CO_2 as the mobile phase (Scheme 33). Under these conditions sequential injection of styrene (**2a**) into the $scCO_2$ flow reactor was analyzed, and the authors reported that even after 7 cycles, no loss of activity nor selectivity was observed.

Additionally, the sequential injections of various olefins were analyzed under $scCO_2$ flow and the results are summarized in Table 1. The alkenes studied were styrene (**1a**), vinyl acetate (**1c**), 1-octene (**1w**), 1-hexene (**1u**), 2,3,4,5,6-pentaflourostyrene ($\mathbf{1d_1}$), and $CF_3(CF_2)_5CH{=}CH_2$ ($\mathbf{1d_2}$) and all of them were successfully hydroformylated with high ees (Table 1).

6 Conclusions

Rhodium is currently the metal of choice to achieve high enantioselectivities in the hydroformylation of a relatively large variety of alkene substrates. Several breakthroughs in this field led to the discovery of several catalytic systems that can nowadays provide high levels of regio- and enantioselectivity for benchmark substrates such as styrene, vinyl acetate, and allyl cyanide.

Furthermore, recent advances have shown that challenging substrates such as alkyl alkenes and internal alkenes can also be converted into the corresponding branched aldehydes with high enantioselectivity by the appropriate choice of catalysts and reaction conditions. However, higher regio- and enantioselectivity can still be achieved when one of the substituents direct the regioselectivity, as is the case of 2,3-dihydrofuran, dihydropyrrol, indene, or 1,2-dihydronaphthalene (Schemes 20 and 22). In the case of symmetrically substituted alkenes such as 2,5-dihydrofuran and norbornene **4o**, **p**, no regiocontrol is required and high activities and enantioselectivities have been achieved in asymmetric hydroformylation (Schemes 20, 21, 23).

1,1-Disubstituted or 1,1,2-trisubstituted substrates are more challenging. The general trend is the introduction of the formyl group onto the less substituted carbon, thus creating the chiral center at the more substituted carbon atom. However, both types of products were formed by Rh-catalyzed hydroformylation with high enantioselectivity and there is still much to learn on the parameters that favor the formation of one regioisomer over another.

In terms of ligands, compounds containing phosphite moieties such as diphosphites and phosphine–phosphites were considered for many years as the most successful ligands to achieve high enantioselectivities. For instance, the phosphite–phosphine BINAPHOS (**40**) or its derivatives **42** and **43** are still today the most successful ligands in terms of selectivity and scope. Recently, however, diphosphines in which the P atoms are incorporated into a ring (**42**–**46**) were also shown to induce high levels of enantioselectivity in this process. It can consequently be concluded that the key to achieve high enantioselectivities is not the type of phosphorus function involved in the coordination to the metal but the particular spatial arrangement of the coordinated ligand.

A variety of chiral products incorporating a formyl unit can be enantioselectively prepared by Rh-catalyzed asymmetric hydroformylation and this process is nowadays considered a powerful tool in organic synthesis and is still a growing area of research. There are still many challenges to be tackled in this area and, for instance, only a few studies including the recovery and recycling of the chiral catalyst have been reported, which could further improve the sustainability of this process and lead to new applications.

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Domino Reactions Triggered by Hydroformylation

Elena Petricci and Elena Cini

Abstract HF reaction represents a selective method for the synthesis of aldehydes starting from alkenes. Because of versatile aldehydes reactivity, it is possible to perform different domino protocols based on contemporary HF, including Michael's reaction, reductive amination, cyclopropanation, lactonization, and many others. This overview reports on the last 5 years' results obtained on this field.

Keywords Cyclohydrocarbonylation · Domino reactions · Hydroaminomethylation · Hydroformylation · Microwaves

Contents

Abbreviations

6-DPPon	6-(Diphenylphosphino)pyridin-2(1*H*)-one
Bcope	Bis(cyclooctyl)phosphine ethane
BISBI	2,2′-Bis(diphenylphosphinomethyl)-1,1′-biphenyl

E. Petricci (✉) and E. Cini
Dipartimento di Biotecnologie, Chimica e Farmacia, Università degli Studi di Siena,
Via A. Moro 2, 53100 Siena, Italy
e-mail: elena.petricci@unisi.it

CTAB	Cetyltrimethylammonium bromide
DPPB	1,4-Bis(diphenylphosphino)butane
HAM	Hydroaminomethylation
HF	Hydroformylation
HFIPA	Hexafluoroisopropanol
MW	Microwave
NAPHOS	2,2'-Bis[(diphenylphosphino)methyl]-1,1'-binaphthyl
NaTPPTS	Sodium triphenylphosphinetrisulfonate
TETRABI	2,2′,6,6′-Tetrakis((diphenylphosphino)-methyl)-1,1′-biphenyl

1 Introduction

Aldehydes are very important functional groups in organic synthesis because of their reactivity and versatility. They are widely employed on the lab scale as well as in process chemistry as intermediates for the synthesis of more complex molecules in pharmaceutical, agrochemical and polymer sciences. Among the plethora of protocols reported in the literature for the preparation of aldehydes, the hydroformylation reaction (HF) represents one of the most useful homogeneously catalyzed processes in industry. Since its discovery in 1938 by Otto Roelen, many improvements in terms of reaction conditions, catalysts, regioselectivity, and compatibility with other functional groups have been achieved ([1] and references cited therein).

As aldehydes are not usually the final product of a general synthesis, the design of domino protocols in which the product obtained by hydroformylation reacts directly with other molecules or functional groups present in the reaction mixture or in a proper position in the starting material represents a hot topic in organic, medicinal, and material chemistry. Domino protocols recently attracted great attention from the scientific community because of their interesting applications in the synthesis of decorated molecules in a step and pot economic way [2–4]. Pellissier recently defined the domino process starting from Tietze's theorization as reactions "involving two or more bond-forming transformations that take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionally formed by bond formation or fragmentation in the previous step [2]." As the aldehydes obtained by HF are usually subjected to further transformations like reductions, oxidations or aldol reactions, they can be considered as the ideal substrates for domino protocols. However, the application of HF reaction in domino transformations is not trivial as the conditions needed for HF are not always immediately compatible with the other transformations, and the formation of by-products often decrease reaction yields. The use of different ligands, and catalysts has taken place in the last few years as an essential outcome in the development of domino HF protocols. The most common ligands developed so far for domino HF are phosphine derivatives (Fig. 1), while Rh and Ru based catalysts are the best metals for HF reactions.

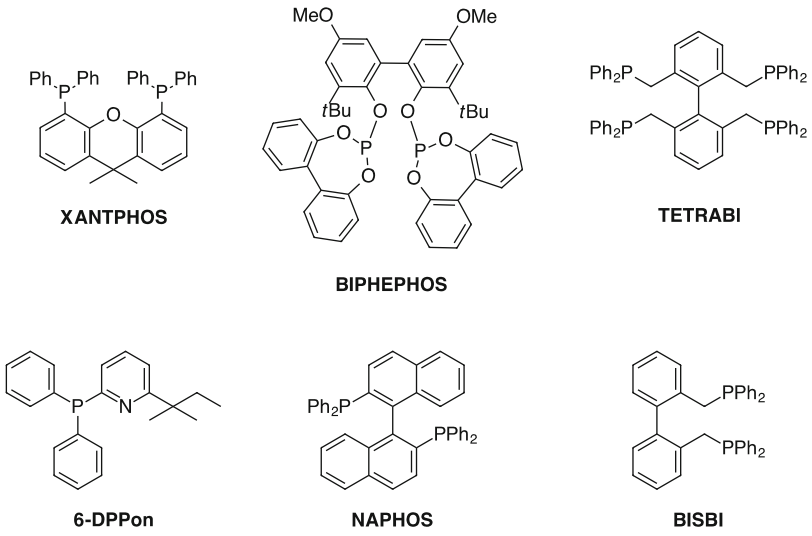


Fig. 1 Ligands for HF reaction

A summary is presented here of the most interesting results achieved in the last 5–10 years in domino processes involving HF as the starting transformation for the activation of the reaction cascades. A review summarizing previous developments in this field was reported by Eilbracht in 1999 [5].

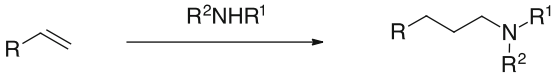
2 Tandem Hydroformylation in the Presence of *N*-Nucleophiles

2.1 Hydroaminomethylation (HAM)

HAM of olefines is an efficient method for the synthesis of various linear and cyclic amines, and it is probably the most used domino process involving HF. Aldehydes generated by HF of alkenes in the presence of amines can be converted on a variety of nitrogen containing products (i.e. Amines, esamines, imines, quinolines,...).

HAM has been efficiently applied to a wide range of substrates using different olefines and *N*-nucleophiles. Although HAM was discovered in 1943 by Reppe [6–8], for long time the reaction suffered from a low regioselectivity with formation of a mixture of linear and branched intermediate aldehydes, as well as polyalkylamines and the products of ordinary hydroamination reactions. After improvements achieved in the last 15 years on HF, it is nowadays possible to consider HAM as a robust and efficient reaction applicable to a wide range of substrates in both inter- and intramolecular versions.

Table 1 HAM of long chain olefines

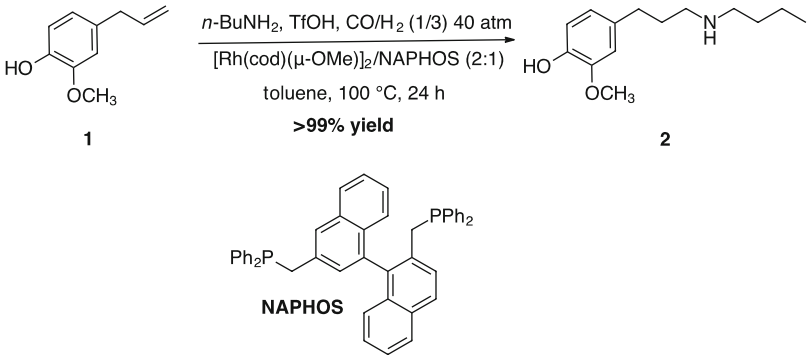


Entry	Alkene	Amine	Catalyst/ligand solvent (time)	*T* (°C)	CO/H_2 (P atm)	Yield (%)	Reference
1	Terminal C_5 up to C_8, styrenes	Secondary	$[Rh(cod)_2]BF_4$/ XANTPHOS MeOH/toluene (1:1), 5 h	125	7/33 (40)	60–99	[9]
2	Terminal C_5 up to C_8	Secondary	$Rh(acac)(CO)_2$/ TETRABI *i*-PrOH/EtOH (2:1), 6 h	125	7/35 (42)	>98	[10]
3	Styrenes	Secondary	$[RhCl(cod)]_2$/ **L1**[a] Toluene, 20 h	70	1/1 (60)	40–85[b]	[11]
4	Eugenol	Primary	[Rh(cod) (μ-OMe)]$_2$/ NAPHOS Toluene, TfOH, 24 h	100	1/3 (40)	>99	[12]
5	Terminal C_6 up to C_{14}	Dimethylamine	RhCl(CO) $(TPPTS)_2$/ NaTPPTS H_2O, CTAB, 6 h	130	1/1 (30)	80–90	[13]
6	Terminal C_6 up to C_{14}	Secondary	RhCl(CO) $(TPPTS)_2$/ BISBIS H_2O, CTAB, 5 h	130	1/1 (30)	90–98	[14]
7	1-Octene	Secondary	$[Rh(cod)]Cl_2$/ NaTPPTS H_2O, H_2SO_4, 4 h	130	1/3 (60)	70–97	[15]

[a]**L1**: tris(3,4,5-trifluorophenyl)phosphine
[b]Branched intermediate aldehydes

An efficient and easy protocol for the HAM of terminal olefines with high regioselectivity has been recently reported by Beller and coworkers, demonstrating that by using cationic rhodium precursors together with commercially available Xantphos as the ligand at 40 atm of syngas, and 125°C for 5 h, is possible to obtain regioselectively linear tertiary amines in good yields (Table 1, entry 1) [9]. The application of the proposed procedure to the synthesis of secondary amines still remains difficult; nevertheless, this report an extensive study on the ligand influence and on the different reaction parameters controlling the overall domino process for further applications on more decorated substrates.

Long chain alkenes are the most studied substrates in HAMs. Good performances can be obtained using the 2,2′,6,6′-tetrakis((diphenylphosphino)-methyl)-1,1′-biphenyl (Tetrabi) ligand associated with $Rh(acac)(CO)_2$ at 42 atm

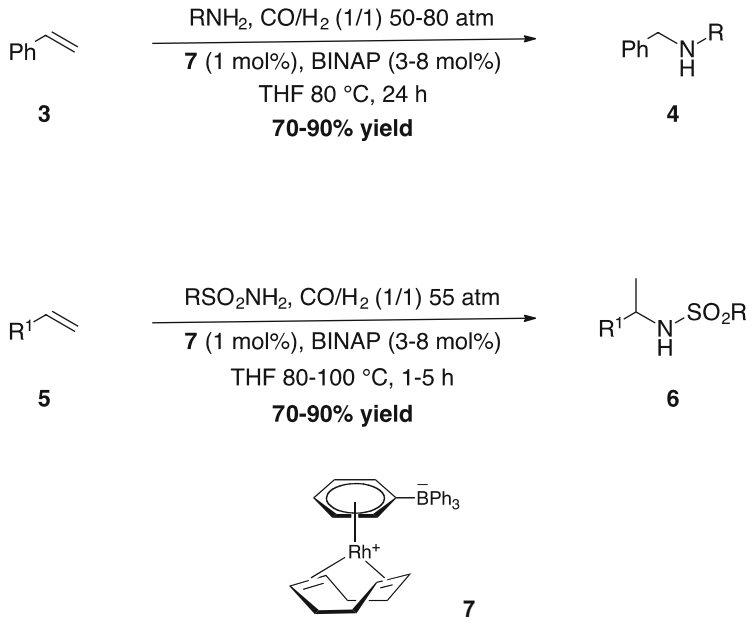


Scheme 1 HAM of eugenol

of CO/H_2 (7:35), 125°C for 4 h; despite the high turnover number of this catalytic system (6930), the short reaction times, great conversions, and regioselectivities obtained, this protocol is limited to secondary amines (Table 1, entry 2) [10]. After many attempts to establish theoretically the properties of a good ligand for HAM of terminal olefines, using DFT calculations associated with experimental data, Clark and coworkers demonstrated the pronounced influence of the phosphine ligands' electronic effect in Rh-catalyzed HAM regioselection. Fluorinated monophosphines are shown to be more effective than their electron-donating counterparts in the hydrogenation of the enamine intermediate coming from HF and secondary amine condensation (Table 1, entry 3) [11].

Santos and coworkers recently reported an interesting contribution on optimization of eugenol (**1**) HAM (Scheme 1) [12]. The problem related to the regioselectivity of the reaction being surpassed by the screening of phosphine ligands, NAPHOS giving the better results. HAM is known to be accelerated in acidic medium and the authors analyzed the influence of different acids. The positive role of the acid used can be directly related to the protonation of the intermediate imine or enamine which can be hydrogenated more easily. On the other hand, the beneficial effect of the acidic medium can in some cases be connected to the formation of cationic Rh active species more efficiently in the hydrogenation of the reaction intermediates. In any case, a key role is played by the different coordination ability of the counter-anions: the stable cationic Rh-complex able to hydrogenate reaction intermediates can be formed only using strong acids, generating poorly coordinating counter-anions. Triflic acid has been demonstrated to be the best promoter for HAM of eugenol in the presence of the electron-donating ligand NAPHOS and $[Rh(cod)(\mu\text{-}OMe)]_2$ in toluene using 40 atm of a 3/1 mixture of H_2/CO at 100°C for 24 h (Scheme 1). Nevertheless, the opposite conclusions in terms of electronic properties of the ligand in HAM in the presence of secondary amines are reported by Clarke and coworkers on different substrates [11].

Biphasic catalytic systems have found interesting applications in the HAM of long chain alkenes with primary amines. A first contribution was reported by Luo, Li and coworkers showing that using water soluble phosphine complexes in the

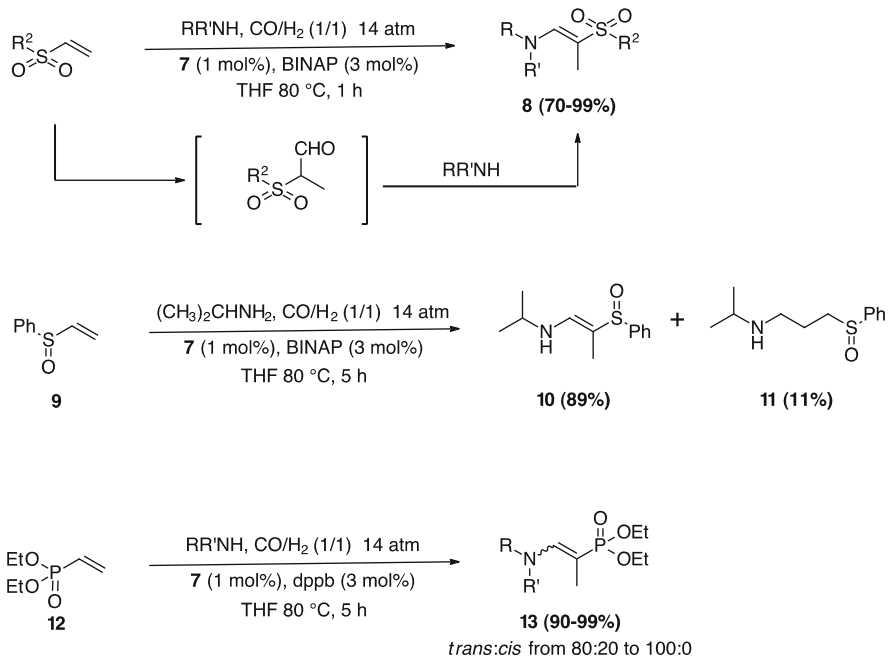


Scheme 2 Synthesis of secondary amines and sulphonamides using BINAP as the ligand

presence of cationic surfactants like cetyltrimethylammonium bromide (CTAB), the HAM of long chain olefines with secondary amines occurs at 30 atm of syngas in H_2O with optimal conversions observed when a 4 to 1 ratio of amine/alkene is used (Table 1, entry 5) [13]. Better results in terms of regioselectivity in HF are obtained using Rh-BISBIS (Table 1, entry 6) [14].

More recently a biphasic protocol has been reported by Behr with an extensive analysis on the influence of different acids on the rate-determining step of the process (hydrogenation of the intermediate enamines) [15]. The catalyst is formed in situ using $[Rh(cod)Cl]_2$ and the water-soluble ligand is sodium-triphenylphosphinetrisulfonate (Na-TPPTS). The effect of adding stoichiometric amounts of various salts of the starting amine has been extensively investigated with the aim of finding a better anion/acid ratio for the hydrogenation of the intermediate enamine (Table 1, entry 7). The acid influence on selectivity seems not to be directly related to the pK_a values, to the use of various secondary and tertiary amines, and to the counterions, influencing the overall process in a more evident way. The effect of different acids in the HAM is now directly correlated to the formation of a new catalytically active species by protonation of the Rh–phosphine system. This cationic Rh complex was shown to be effective in the hydrogenation of imines; by contrast, alkenes are only hydrogenated to a slight extent, decreasing this typical HF by-product.

In the search for easily available Rh ligands, BINAP has emerged in the last few years as a good choice for application in both intra- and intermolecular HAMs. Alper and coworkers reported the possibility to obtain regioselectively linear



Scheme 3 HAV of vinylsulfones, vinylsulfoxides and vinylphosphonates

secondary amines **4** and sulphonamides **6** using the zwitterionic Rh complex **7** in the presence of BINAP (Scheme 2) [16].

The same catalytic mixture is found to be effective for the one-pot hydroaminovinylation (HAV) of vinylsulfones and vinylsulfoxides while vinylphosphonates give better results in terms of reaction yields and regioselectivity, using DPPB as the ligand (Scheme 3) [17]. Vinylsulfoxides can be subjected to HAV only with primary amines, and without complete regioselectivity in the HF step. Both vinylsulfones and vinylphosphonates furnish branched aldehydes as the only products of HF, while sulfonaldehydes react with primary and secondary amines to produce the *E* derivatives **8**; phosphonaldehydes show a lower regioselectivity in the HAM conditions developed so far.

HAM is a domino process involving two steps catalyzed by the same metal. However, orthogonal catalysis has been successfully applied by the addition to the reaction mixture of two precursors of the catalytic species involved in the HF, the hydrogenation steps not interfering with each other. The use of an Rh catalyst for HF with an Ir complex for the imine hydrogenation is the most common strategy reported so far. Although Rh species are usually able to catalyze both transformations, the involvement of a different complex in each catalytic process has been demonstrated [18]. Webersikirch investigated the possibility of using a tailor-made dual heterogeneous Rh/Ir systems to catalyze HAM of terminal olefines, Rh being suitable for the HF and Ir for the selective reduction of the enamines (Fig. 2) [19]. Despite the wonderful results obtained using

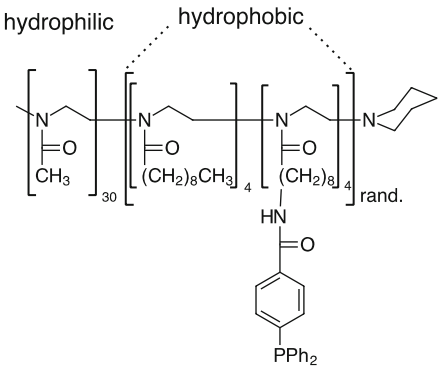
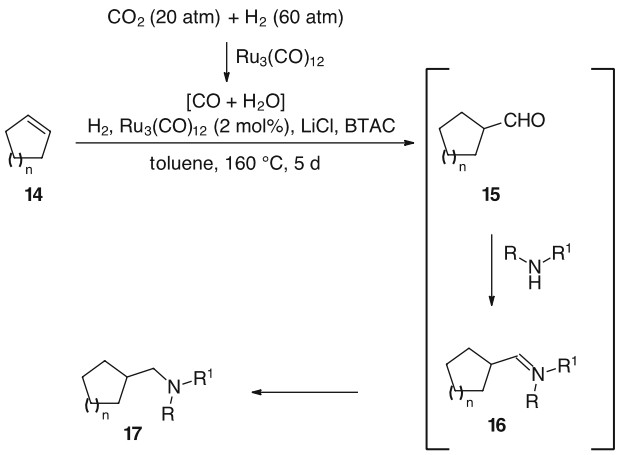


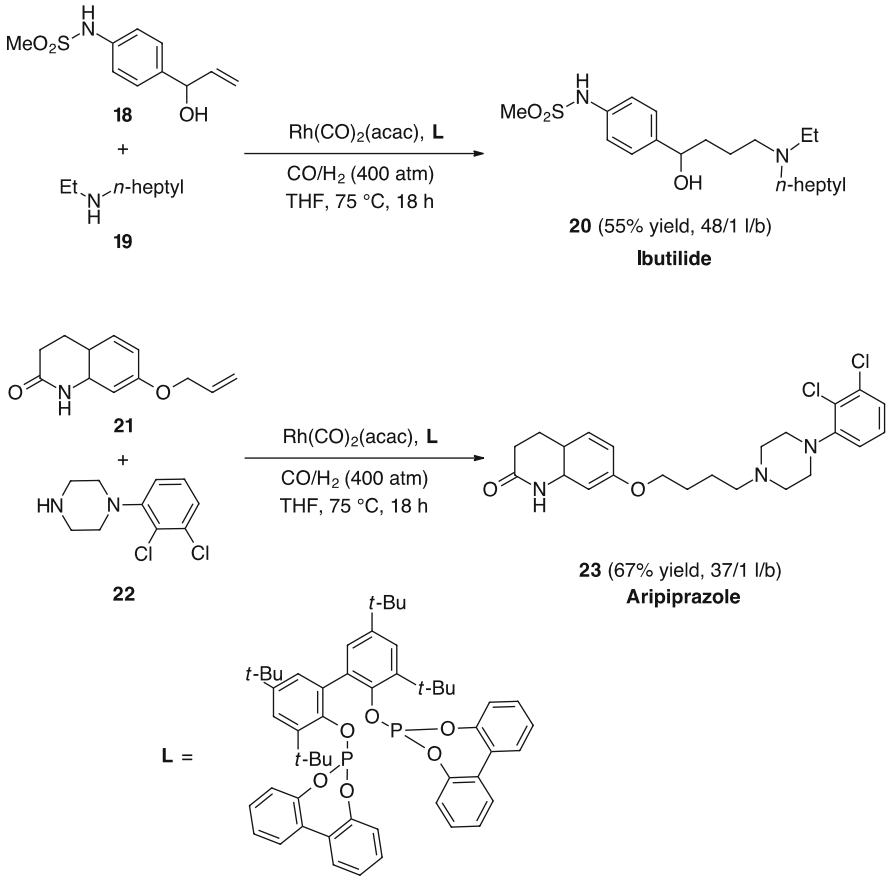
Fig. 2 Amphiphilic, triphenylphosphine functionalized poly(2-oxazoline) block copolymer



Scheme 4 HAM using Ru catalysis and CO_2 as CO source

Rh triphenylphosphine functionalized poly(2-oxazoline) block polymers in the HF of octene, under HAM conditions a mixture of the aldehyde, enamine, and the expected product was observed. The development of this new bimetallic system enable one to obtain good conversions at 130°C, and even if the protocol needs further optimization this is the first report demonstrating that a nano-reactor approach based on polymeric micelles can be considered as a possible alternative to established technologies. This result demonstrates that application in complex reaction sequences that require tailor-made multi-metal catalysts are possible.

While Morimoto developed a syngas free HF protocol using formaldehyde as the CO/H_2 source [20], Eilbracht investigated the possibility of replacing toxic CO with carbon dioxide using $Ru_3(CO)_{12}$ as the catalyst [21]. The protocol proposed starts with the reduction of CO_2 with H_2 in the presence of a proper Ru complex forming the CO necessary for HF and H_2O. Under these unusual conditions, the HAM of cyclic alkenes occurs in the presence of both primary, and secondary amines. Working

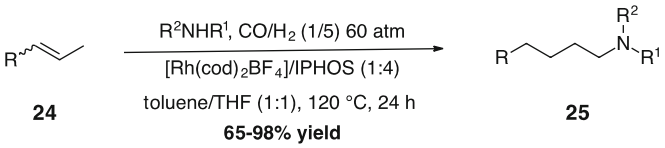


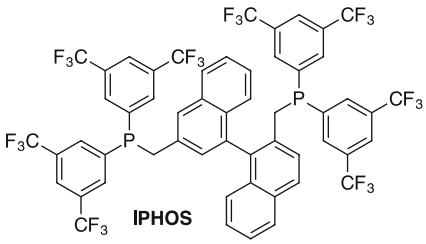
Scheme 5 HAM for the synthesis of ibutilide, and aripiprazole

with an excess of alkene and primary amines, the product obtained was a 2:1 mixture of tertiary and secondary amines. During the reaction the formation of water occurs, giving a biphasic mixture. Consequently, the addition of benzyl triethyl ammonium chloride (BTAC) as a phase transfer catalyst in the presence of LiCl has a beneficial effect suppressing the formation of common by-products like alcohols and alkanes (Scheme 4). The protocol suffers from a general low regioselectivity in terms of linear/branched aldehydes formed using terminal alkenes; the development of new ligands for the Ru catalysts should help to surpass this limit.

HAMs protocols have even been applied to the synthesis of a wide range of biologically relevant structures. Using an Rh-bisphosphite catalyst, ibutilide **20** and aripiprazole **23** have been regioselectively prepared in good yields and large scale working at a relatively high pressure of syngas (400 atm, Scheme 5) [22].

A fundamental improvement on HAM is the recent possibility to obtain linear amines starting from internal olefines. Very recently, Beller and coworkers reported





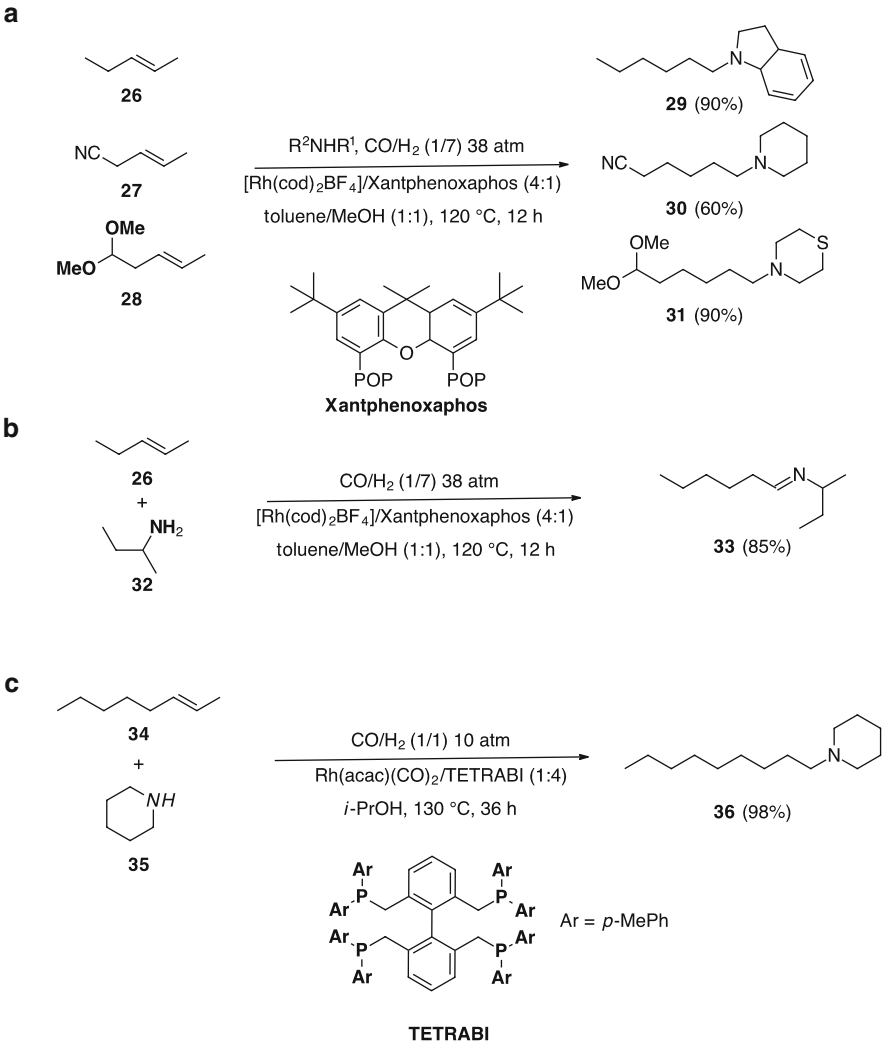
Scheme 6 HAM of internal olefines to linear amines

Table 2 Regioselective HAM of internal olefines

Entry	Alkene (functional groups)	Amine	Catalyst/ligand solvent (time)	*T* (°C)	CO/H_2 (P atm)	Yield (%)	Reference
1	2-Alchenes C_5 up to C_8	Piperidine	$Rh(acac)(CO)_2$/ TETRABI *i*-PrOH, 36 h	130	1/1 (10)	60–99	[25]
2	2/3-Alchenes C_5 up to C_8 (CN, OMe, OH)	Secondary	$[Rh(cod)_2]BF_4$/ Xantphenoxaphos Toluene/MeOH (1:1), 12 h	120	1/7 (38)	60–90	[24]
3	2-Pentene	Piperidine	$[Rh(cod)_2]BF_4$/ Isopropxantphenoxaphos Toluene/MeOH (1:1), 12 h	125	1/5 (40)	70	[24]

the first catalytic protocol to achieve a high regioselective hydroaminomethylation of internal alkene [23]. The catalyst proposed is a Rh based complex with IPHOS that immediately isomerizes the internal double bond, regioselectively hydroformylates it, and finally reduces the intermediate enamine or imine obtained by reaction of the aldehyde with a proper amine (Scheme 6). The main achievement of this protocol is related to the high regioselectivity of both isomerization and HF reactions.

After a first contribution, the protocol developed was successfully modified with the screening of different ligands finally enabled the use of less drastic conditions in terms of reaction temperature, pressure of CO/H_2, and reaction times with respect to the first proposed protocol (Table 2) [24]. The bite angles of the ligands have a dramatic effect on the both chemo- and regioselectivity of the reaction. Using XANTHPHOS-type or TETRABI ligands the HAM of internal alkenes can now be applied even to sophisticated substrates, showing a high versatility and large

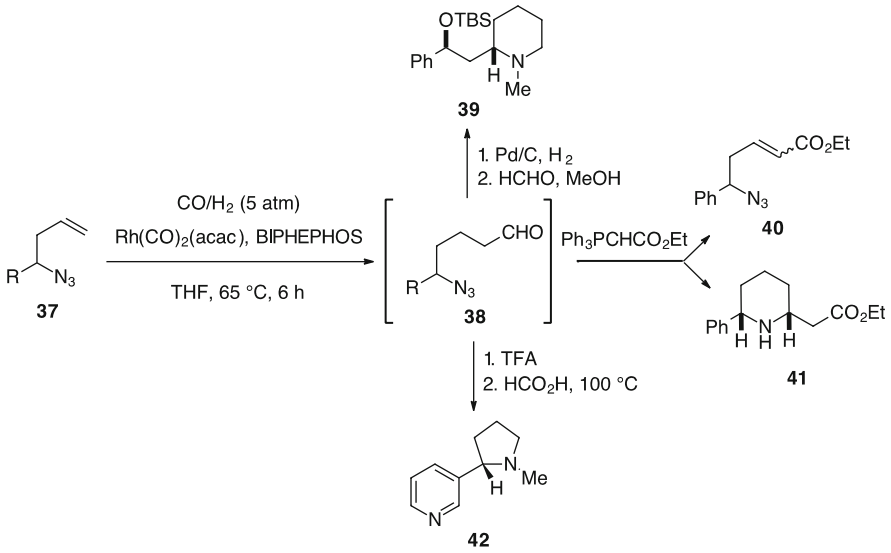


Scheme 7 Regioselective HAM of internal olefines

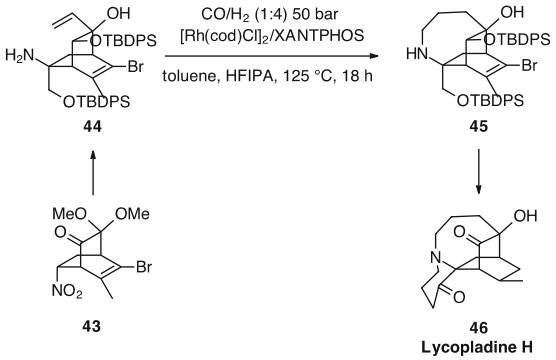
applicability to the synthesis of different molecules [25]. When primary amines are used as nucleophiles, imines are isolated as the only product (Scheme 7).

2.1.1 Intramolecular HAM

The design of proper starting material plays a fundamental role in the development of intramolecular HAM protocols for the diversity oriented synthesis of chemically and biologically interesting heterocyclic compounds. Mann and coworkers have recently planned an HAM protocol where the nitrogen nucleophile is generated in



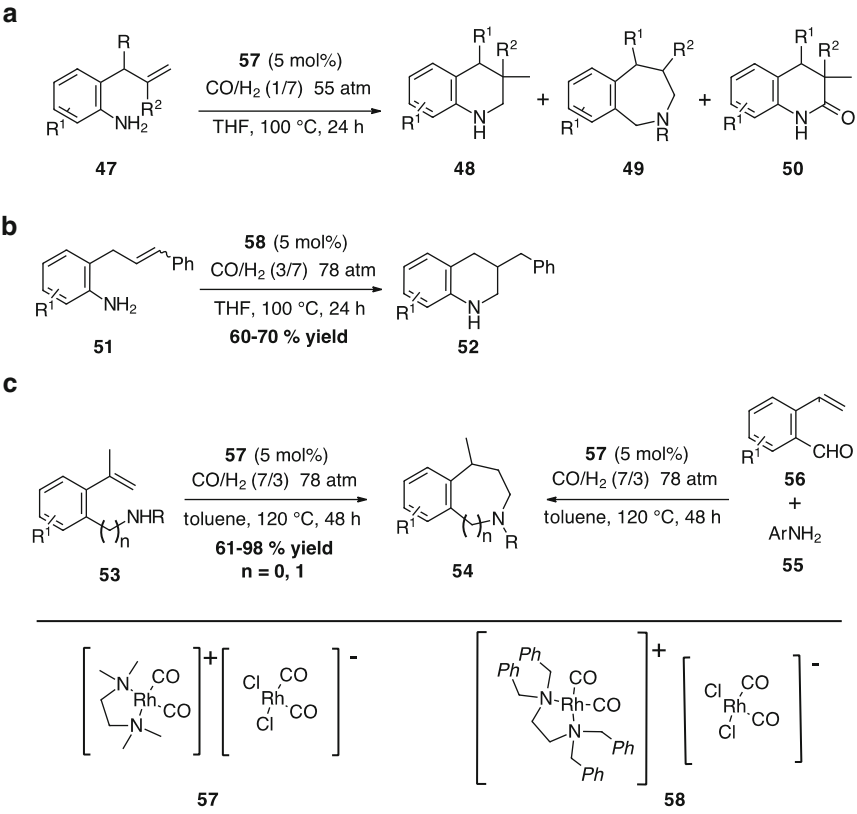
Scheme 8 HF of homoallylic azides



Scheme 9 HAM for the synthesis of lycopladine-H

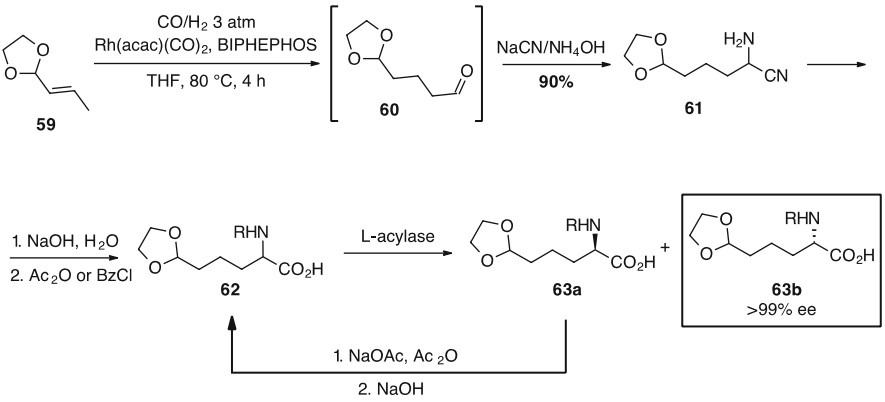
situ by reduction of an azido group inserted in a proper position on the staring material. The HF of homoallylic azides enables rapid access to alkaloids in an efficient, atom economic way in a tandem sequence involving the sequences HF/reduction or HF/Wittig reaction/reduction (Scheme 8) [26].

Intramolecular HAM has been efficiently applied to the synthesis of lycopladine-H **46**, a natural product containing an azocane moiety which is difficult to synthesize. This protocol can be extended to all lycopodium alkaloids giving easy access to this class of biologically active alkaloids [27]. It is interesting to note that in this transformation the use of hexafluoroisopropanol (HFIPA), a protic non-nucleophilic slightly acid solvent, appears to be fundamental to enhance cyclization yields and selectivity (Scheme 9).



Scheme 10 Intramolecular HAM of allylanilines

Rhodium diamine complexes were demonstrated to be effective catalysts for the intramolecular HAM of 2-allylanilines **47** and **48**, or properly functionalized benzylamines **53** (Scheme 10). The intramolecular HAM of 2-allylanilines using the catalyst **57** gave a mixture of products in different ratios depending on the starting substrate (Scheme 10 [a]) [28]. 1,2,3,4-Tetrahydro-3-benzylquinolines can be synthesized as well by HAM of anilines when an internal alkene is present in the lateral chain, **58** proving to be the best catalyst in the presence of 78 atm of CO/H_2 (3/7) in THF at 100°C for 24 h (Scheme 10 [b]) [29]. Finally, complex **57** also catalyzed the high yield regioselective synthesis of 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepines starting from aniline and 2-vinylbenzylamines **53** or 2-vinylbenzaldehydes **56**, (Scheme 10 [c]) [30]. Moreover, starting from 2-styrylanilines, substituted 1,2,3,4-tetrahydro-4-methylquinolines were obtained in the same reaction conditions with optimal yields and regioselectivities [29, 30].

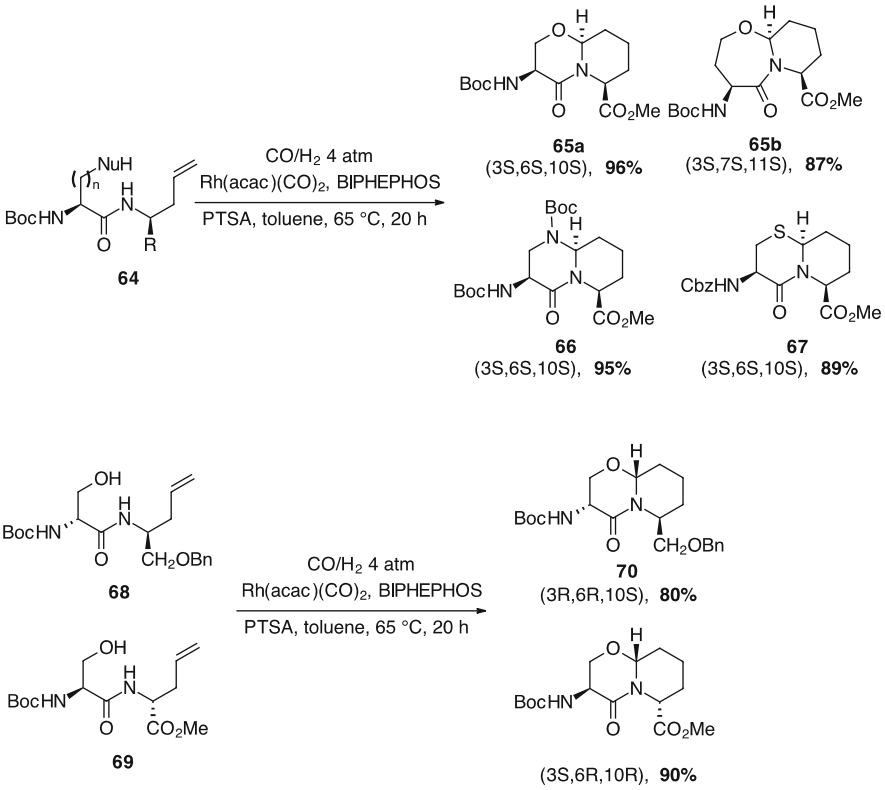


Scheme 11 Large-scale synthesis of (*S*)-allysine ethylene acetal

The combination of HF with the Strecker reaction has been efficiently applied in combination with biocatalysis for the large-scale synthesis of (*S*)-allysine ethylene acetal **63b**, a key intermediate in the synthesis of different angiotensin-I converting enzyme and neutral endopeptidase inhibitors, currently in clinical trials [31]. It is interesting to note that this protocol starts from the internal alkene acetal **59** obtaining regioselectively in situ the linear aldehyde that was subjected to Strecker reaction with formation of the amino nitrile **61** in 90% yield. Once the amino nitrile is formed the transformation into the corresponding amino acid, followed by acetylation and enzymatic resolution with L-acylase, furnished the expected product in a very effective way (Scheme 11).

2.2 *Cyclohydrocarbonylation (CHC)*

As previously indicated, HAM allows easy access to decorated amines in an efficient and atom economic way by hydrogenation of an intermediate imine or enamine species. Imine as well as enamine groups are particularly reactive, and the reaction cascade of HAM can be controlled to produce selectively these moieties which can further react with proper nucleophiles present in the reaction mixture. This transformation is known as CHC when a decorated heterocyclic or polyheterocyclic compound is formed. Ojima has pioneered CHC over the last 20 years, developing methodologies for the synthesis of several biologically interesting molecules [32–34]. A typical Ojima CHC protocol consists of: (1) a linear-selective hydroformylation of a terminal alkene; (2) an intramolecular condensation to form a cyclic *N*-acyliminium key intermediate, followed by (3) a second cyclization through an intramolecular nucleophilic addition of a heteroatomic or carbon nucleophile to afford



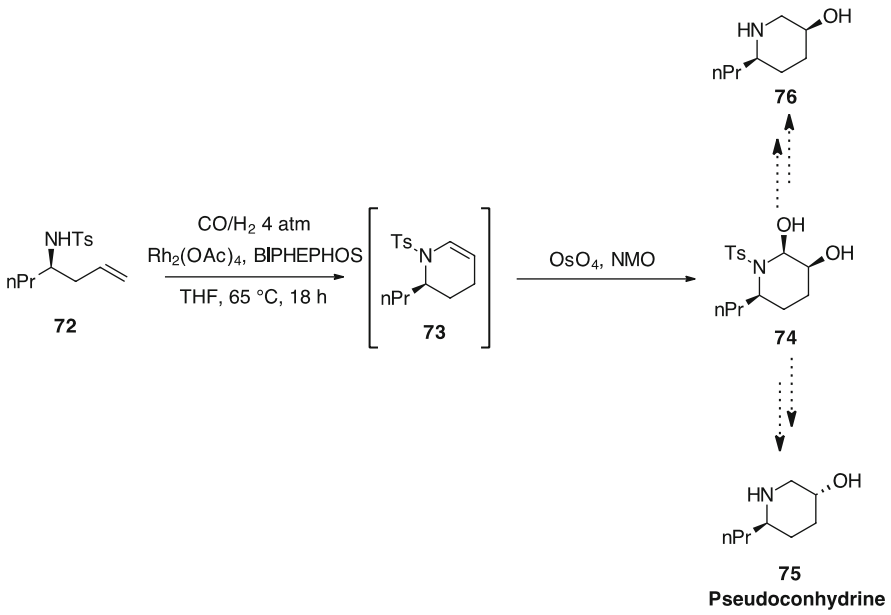
Scheme 12 CHC in the synthesis of bicyclic compounds starting form dipeptides

the corresponding 1-azabicyclo[x.y.0] system [35]. Starting from a properly functionalized dipeptide **64**, new bicyclic compounds **65–67** are obtained. A new stereogenic centre is formed in a very stereocontrolled way by the assistance of the substituent in the C-10 position on the final product (Scheme 12). Good results are observed using oxygen, nitrogen or sulphur nucleophiles.

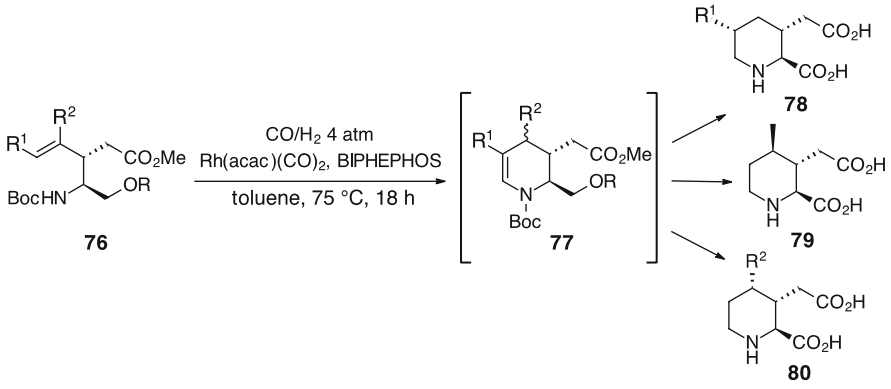
In both cases the use of BIPHEPHOS, and $Rh(acac)(CO)_2$ in the presence of a catalytic amount of PTSA gives the best results.

A CHC can be used for the synthesis of pseudoconhydrine **75** and its epimers **76** (Scheme 13) [36]. A starting homoallylic amine derivative **72** can be subjected to an HF-condensation sequence combined with oxidation of the intermediate enamine derivative. By treating **72** with $Rh_2(OAc)_2$, BIPHEPHOS, under 60 atm of CO/H_2 at 65°C for 18 h, **73** is obtained in high yield and good regioselectivity and can be reacted in situ with OsO_4 to give diastereoselective access to **74**, an interesting precursor of pseudoconhydrine.

A quite similar protocol has been used for the synthesis of 3-hydroxypipecolic acid derivatives [37] and homokainoids (Scheme 14) [38].



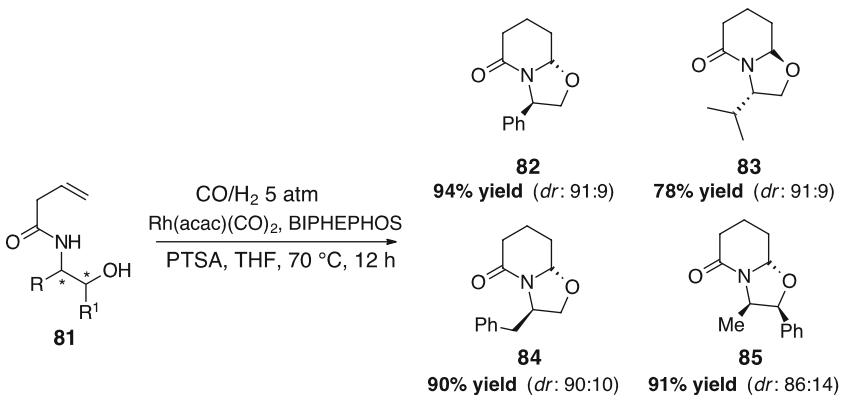
Scheme 13 Synthesis of pseudoconhydrine



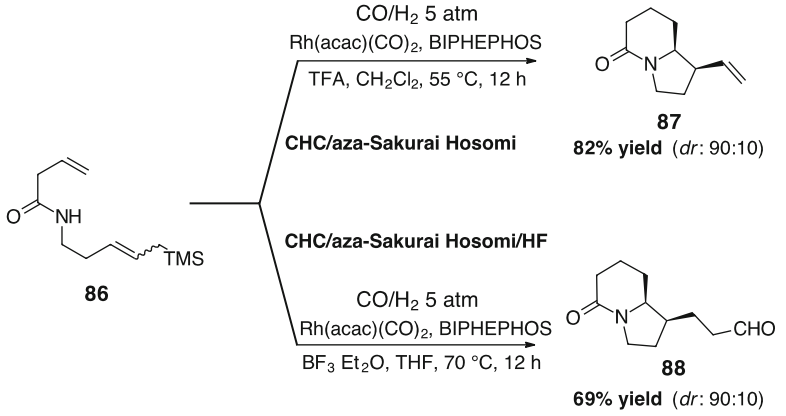
Scheme 14 CHC in the synthesis of 3-hydroxypipecolic acid derivatives and homokainoids

Mann and Taddei widely explored CHC for stereoselective synthesis of heterocyclic compounds in cascade with other transformations such as: CHC/aza-Sakurai Hosomi, CHC/aza-Sakurai Hosomi/HF, and CHC/Pictect–Spengler [39]. Proper design of the starting materials, obtained by decoration of 3-butenoic acid with different chiral auxiliaries, enables a certain control on the new stereogenic centres generated during the reaction cascade.

Starting from the chiral aminoalcohols **81**, using $Rh(acac)(CO)_2$ as the catalyst and BIPHEPHOS as the ligand in THF with a catalytic amount of PTSA at 5 atm of



Scheme 15 Use of chiral aminoalchols in CHC

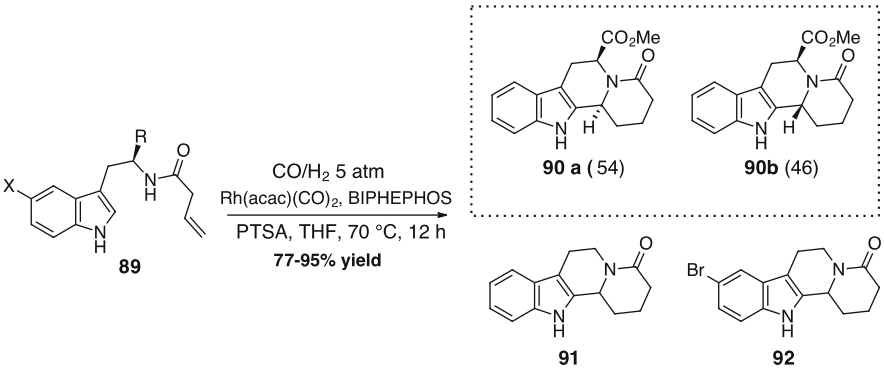


Scheme 16 CHC in domino with Aza-Sakurai Hosomi reaction

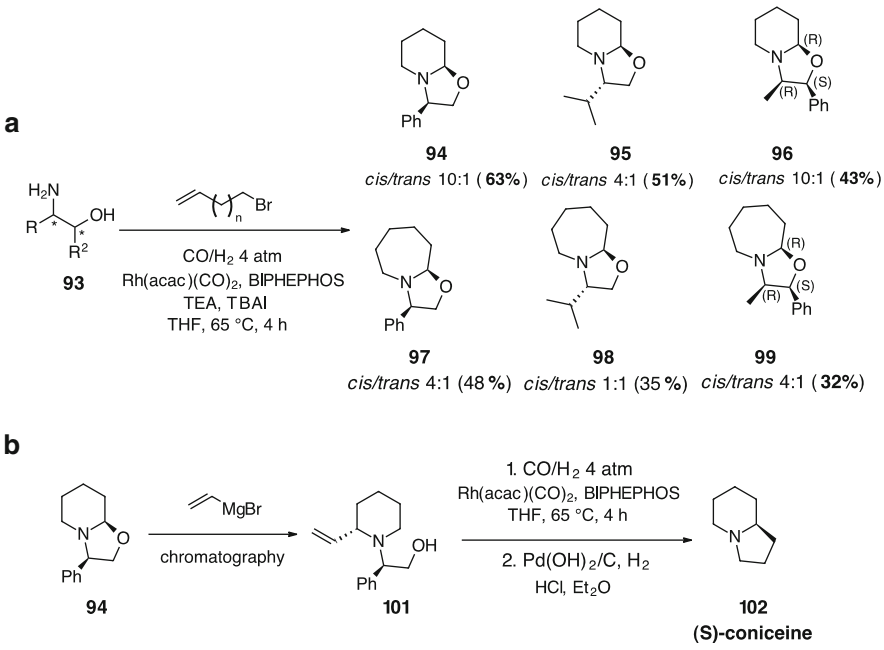
syngas, bicyclic compounds **82–85** are obtained with excellent yields and good stereoselectivity (Scheme 15) [39].

The nucleophilic reactivity of allylsilane in CHC has been studied as well, with good results. The chemoselective HF of **86** in CH_2Cl_2 and TFA at 55°C for 12 h affords an intermediate enamide which directly undergoes an Aza-Sakurai Hosomi's reaction with the formation of **87** in good yield and stereoselectivity. Working in the same reaction conditions, just changing the acid (BF_3 OEt_2) and the solvent (THF) used, a further HF of **87** occurs, **88** being isolated as the only reaction product (Scheme 16) [39]. With the developed protocols, two cycles and nine new bonds are formed in the same chemical operation.

The same group investigated the possibility of using CHC in domino with Pictect–Spengler reaction. It is interesting to note that, starting from indole derivatives **89**, N-containing polycyclic compounds **90–92** can be obtained by just carrying out



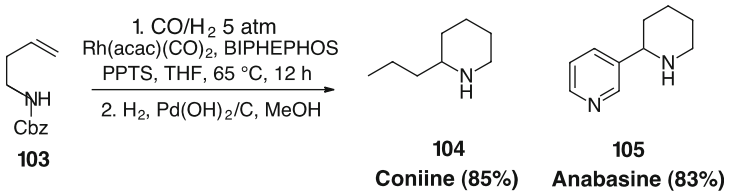
Scheme 17 CHC in domino with Pictect–Spengler reaction



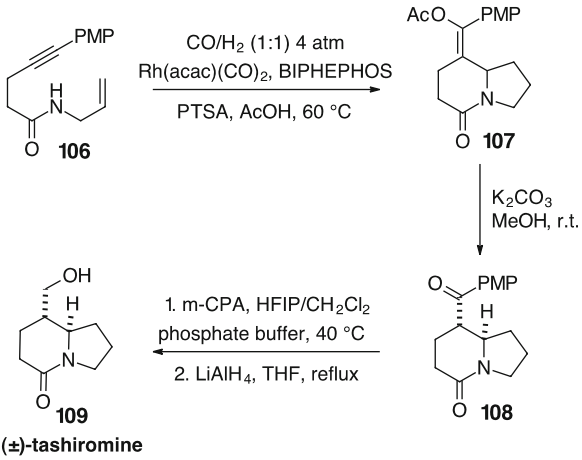
Scheme 18 Synthesis of oxazolopiperidines

the HF protocol in the presence of PTSA (Scheme 17). However, this protocol suffers for a less than excellent diastereoselectivity in the conditions reported so far.

When a chiral aminoalcohol **93** is used as the starting material in the presence of bromoalkenes under HF conditions ($Rh(acac)(CO)_2$, BIPHEPHOS, TEA, TBAI, THF) a mixture of epimer oxazolopiperidines is obtained, the *cis* compound being the main diastereoisomer formed (Scheme 18 [a]) [40]. Compound **101** can be used as the starting material for the synthesis of (*S*)-coniceine **102** where a tandem process involving HF is essential (Scheme 18 [b]).



Scheme 19 Synthesis of coniine and anabasine



Scheme 20 Alkyne mediated CHC

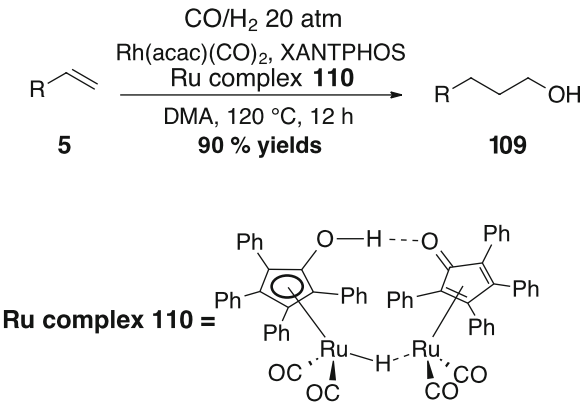
CHC also proved to be helpful in the total synthesis of many natural products like coniine **104**, anabasine **105** [26], crispine A [41] (Scheme 19), and many other indolizidine alkaloids (for a review on the use of domino HF protocols in natural products synthesis see [42]).

Between the CHC protocols applied to the synthesis of natural products, the double cyclization mediated by an alkyne moiety reported by Chiou appears to be particularly interesting, giving access to (±)-tashiromine **109** (Scheme 20) [43].

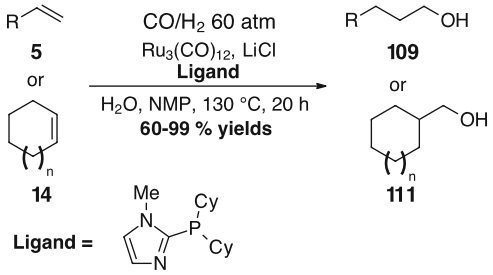
For a more detailed review of the application of HF reaction in natural products synthesis see the specific Settambolo's contribution in this issue.

3 Domino HF/Reductions

Domino HF and hydrogenation reactions are widely applied methodologies for the synthesis of alcohols using different phosphine ligands and catalysts (i.e. Co [44], Rh [45], Ru and Pd [46]). Supramolecular Rh catalysts have been used independently by Breit [47] and Cole-Hamilton [48], giving linear alcohol in 72% and 87% yields, respectively. In these, only one metal is used as the catalyst for two different



Scheme 21 Synthesis of alcohol using a Rh/Ru dual catalyst system



Scheme 22 Use of $Ru_3(CO)_{12}$ in domino HF/reduction protocols

reactions although under drastic reaction conditions. The Rh/Ru dual catalyst **110** system has been developed to obtain high regioselectivity and yields using *N*,*N*-dimethylacetamide (DMA) as the solvent at 120°C for 12 h in the presence of 20 atm of syngas (Scheme 21) [49]. In this protocol, $Rh(acac)(CO)_2$ and XANTPHOS form the catalytically active specie for the HF, while Ru complex produces the reduction of the aldehyde.

A similar Rh/Ru dual catalyst has been proposed for this transformation by Bhanage and coworkers [50]. In this case, a tandem protocol is developed where the HF runs under classical Rh/PPh_3 complex in an ionic liquid supported on silica, using water as the reaction medium in the presence of 50 atm of syngas (80°C, 5 h), and the aldehyde hydrogenated (50 atm of H_2) by adding Ru/PPh_3 catalyst supported on silica at 100°C for 4 h. This protocol offers several advantages such as the use of an inexpensive easily available ligand (PPh_3), a simple work-up, and mild reaction conditions; nevertheless, still being a tandem protocol, it suffers from a low regioselectivity with respect to Breit's method. More recently, starting from Pakkanen's observations [45], Beller and coworkers extended the use of $Ru_3(CO)_{12}$ to domino HF/reduction of difficult substrates as internal alkenes; the main challenge introduced is related to the use of ligands able to give better conversions in shorter reaction times, and particularly high regioselectivities (Scheme 22) [51].

It is interesting to note that both Pakkenen's and Beller's studies highlight a challenging point in hydroformylation catalysis: despite what was previously thought, Ru can be considered an effective metal for carbonylation reactions, opening a new era on these transformations. In our opinion, the main limitation to be overcame on the use of Ru catalyzed HF is related to its activity on hydrogenation reaction; it can actually be considered as a good choice for the synthesis of alcohols but not for aldehydes, and the development of proper ligands for the tuning of its reactivity may be an interesting area for further research.

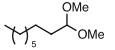
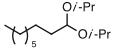
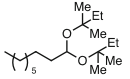
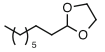
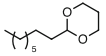
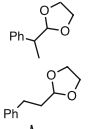
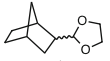
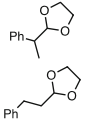
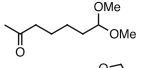
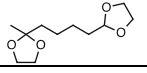
Alcohols can be obtained in a domino isomerization/HF/hydrogenation sequence, even using an uncommon metal for HF reactions like Pd. Leñero and coworkers reported the possibility of combining $[Pd(OTF)_2(bcope)]$ with NaCl to convert selectively linear internal and terminal alkenes into linear alcohols under 105°C at 60 atm of CO/H_2 (1:2) in 5 h [52]. The halide anion proves to have a crucial effect on the rate of HF and on both chemo- and regioselectivity, the level of effect on regioselectivity being seen in linear alcohol to be $I^- > Br- > Cl^-$ and on reaction rate to be $Cl^- > Br^- > I^-$.

4 Tandem HF in the Presence of *O*-Nucleophiles

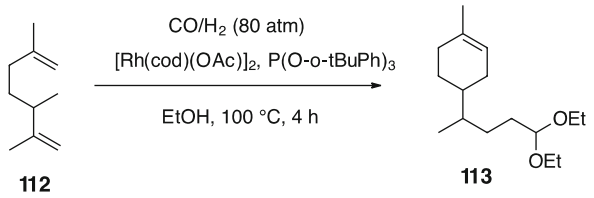
Acetal formation is a typical reaction of aldehydes in the presence of alcohols. The possibility of running HF in the presence of alcohols in the reaction mixture has been widely explored in both inter- and intramolecular versions, trapping unstable aldehydes masking this functional group as well as generating decorated lactols in an atom economic way. Lactols are interesting intermediates in organic [53–55] and natural products synthesis [56–58]. HF of properly designed starting materials with an OH group in a suitable position represents an interesting opportunity for the synthesis of functionalized lactols.

Acetals can be efficiently formed by HF of both terminal and internal alkenes as well as alkynes in the presence of primary alcohols or diols using $[Rh(cod)_2]BF_4$ and XANTPHOS at 110°C for 1 h under 30 atm of a 1:2 mixture of CO/H_2 (Table 3) [59]. After an extensive study of reaction parameters it can be concluded that: (1) the acetal selectivity decreases from primary to tertiary alcohols; (2) many diols can be used for the synthesis of cyclic acetals in an efficient way even if (3) the reaction with internal alkenes is very slow needing the use of $P(OP)_3$ as the ligand; (4) phenylacetylene proved to be a good substrate, this reaction forming saturated acetals, which suggests an HF-acetalization-hydrogenation cascade; (5) small amounts of water are tolerated; and (6) the high selectivity observed can be related to the cooperative effect of rhodium species and the HBF_4 formed in situ from the catalyst precursor. It is interesting to note that starting from allylacetone in MeOH the acetalization selectively occurs on the aldehyde moiety (Table 3, entry 10); in contrast, in ethylene glycol the acetal formation is faster, achieving the corresponding diacetal (Table 3, entry 11).

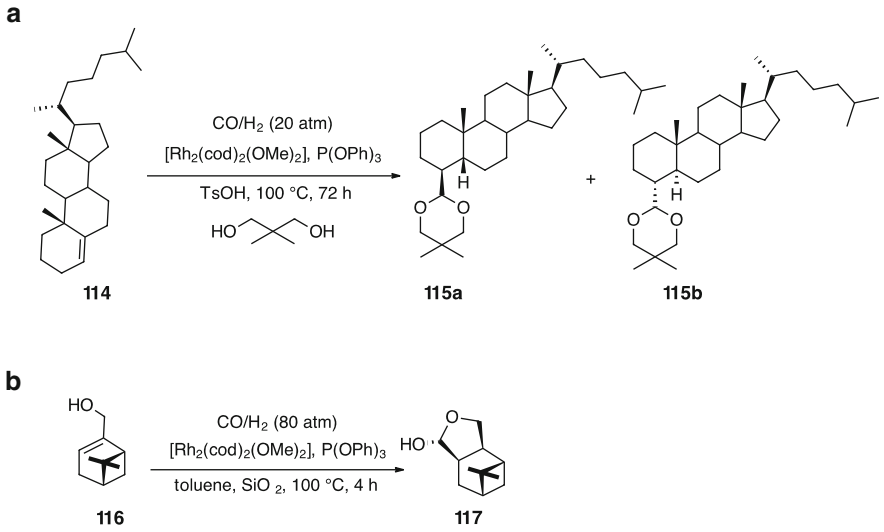
Table 3 Domino HF/acetalization conditions

Entry	Alkene	Alcohol	Product	Conv. (%)[a]	Acetal selectivity (%)	l/b ratio
1	1-Octene	MeOH		86	92	52
2	1-Octene	*i*-PrOH		88	69	89
3	1-Octene	2-Mebutan-1-ol		83 (93)[b]	6.9 (<0.5)[b]	17
4	1-Octene	$HOCH_2CH_2OH$		70	99	26
5	1-Octene	$HOCH_2CH_2CH_2OH$		92	94	9
6	Cyclooctene	$HOCH_2CH_2OH$		27 (98)[c]	99	–
7	Styrene	$HOCH_2CH_2OH$		97 (98)[d]	91 (97)[d]	1 (0.31)[d]
8	Norbornene	$HOCH_2CH_2OH$		>99	92	8.6
9	Phenylacetylene	$HOCH_2CH_2OH$		91	97	2.5
10	Allylacetone	MeOH		>99	85	21
11	Allylacetone	$HOCH_2CH_2OH$		84	51	7

[a]Reaction conditions: $[Rh(cod)_2]BF_4$, Xantphos, CO/H_2 (1:2) 30 atm, 110°C, 90 min
[b]Reaction conducted at 140°C
[c]$P(OPh)_3$ used as ligand
[d]PPh_3 used as ligand



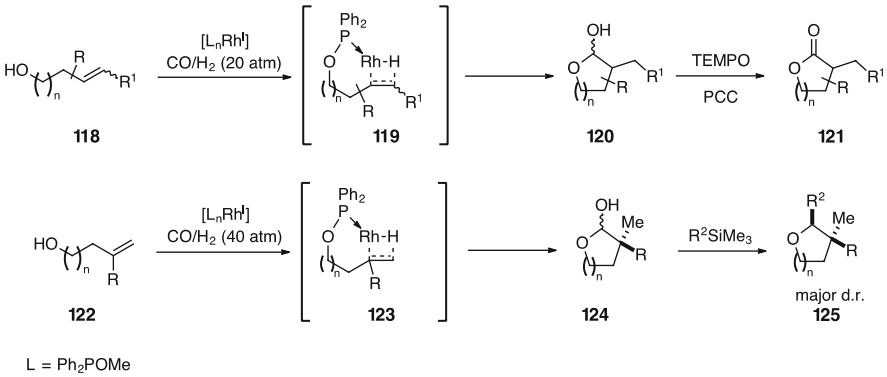
Scheme 23 Use of HF/acetalization domino protocols on terpenes



Scheme 24 Use of domino HF/acetalization for the homologation and protection of steroids and (−)-myrtenol

Rhodium catalyzed domino HF/acetalization has been studied on a series of *p*-menthenic terpenes (i.e. α-terpinene, γ-terpinene, terpinolene and limonene) in EtOH solutions. P(O-*o*-*t*BuPh)$_3$ was the most versatile and efficient ligand, accelerating the acetalization step (Scheme 23) [60]. The main limitation of this protocol is a scarce selectivity observed when more than one double bond is present in the substrates. However, a certain tuning of HF is possible by changing the Rh/ligand ratio. Starting from limonene, HF and subsequent acetalization occur only on the terminal alkene.

When aryl alkenes and different alcohols were heated for 6 h at 80°C in the presence of $RhCl_3$, and P(OPh)$_3$ under 40 atm of syngas, branched, linear and cyclic acetals were obtained with good yields and selectivities [61]. Even complex substrates such as steroids (**114** in Scheme 24) can be subjected to HF and domino acetalization, giving a 1:1 mixture of **115a** and **b** with complete regioselectivity and good yields (Scheme 24 [a]) [62]. When (−)-myrtenol was treated in analogous reaction conditions, the stereoselective formation of the cyclic hemiacetal **117** was observed (Scheme 24 [b]).



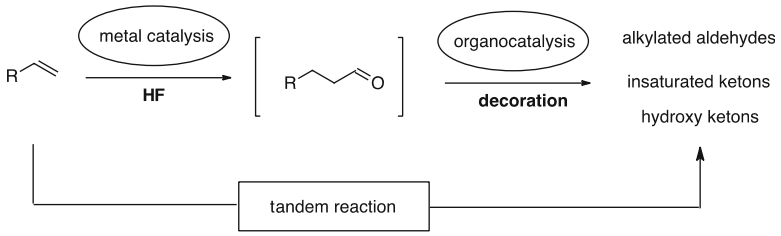
Scheme 25 Synthesis of γ-lactols and lactones

Terminal and internal bishomoallylic alcohols can HF with high regio- and diastereoselectivity, employing a catalytic amount of a catalyst-directing group, enabling atom-economical preparation of a wide range of γ-lactols and lactones (Scheme 25) [63].

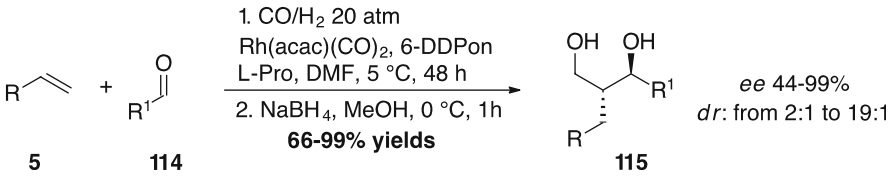
This protocol is particularly suitable as the directing group is bound in the farthest position ever reported so far; reaction conditions requested are mild (20 atm of syngas, 60°C, 12 h), and simple Ph_2POMe is used both as the ligand and the directing group. Coupling the HF and lactol formation with a tandem oxidation in the presence of PCC or TEMPO, lactones are obtained in high yields and diastereoselectivity. The methodology can be properly extended to the synthesis of tetrahydrofurans [64].

5 HF Domino with Organocatalytic Process

Multicatalyst promoted asymmetric domino reactions recently emerged as a powerful tool for the synthesis of decorated organic molecules in an efficient way. The development of an integrated metal- and organo-catalytic integrated protocol represents a big challenge because of the difficulties related to the research of the optimal and compatible reaction conditions required for the planned transformations. Among these integrated cascade reaction protocols developed in the last few years, those able to generate new C–C bonds in an atom economic way represent a charming tool in organic synthesis, but only a few protocols involving HF reaction have been reported so far. The Lewis base catalysis of organocatalytic processes and the empty coordination site needed by metal complexes in HF are, in principle, incompatible. Nevertheless, aldehydes are fundamental functional groups for several organocatalytic processes (i.e. Michael reaction, aldol condensation, cyclopropanation, Knovenagel condensation, Mannich type reactions) and



Scheme 26 HF domino with organocatalytic process



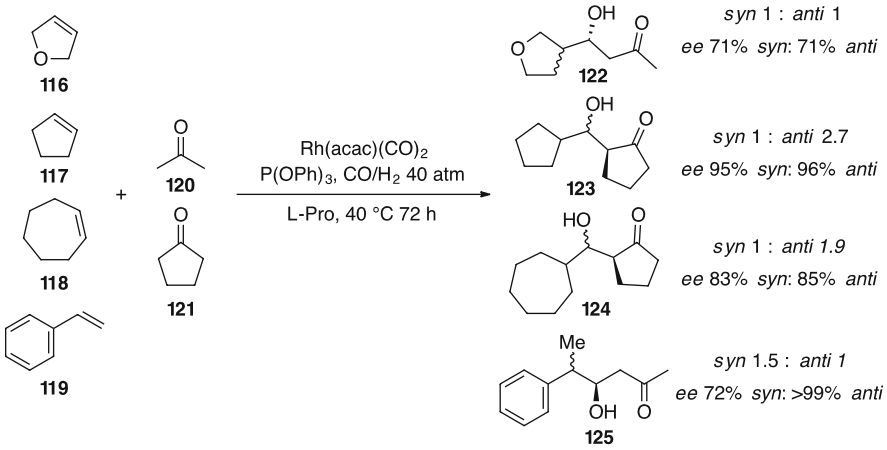
Scheme 27 Stereoselective synthesis of diols

consequently the development of domino metal and organocatalysts mediated transformations is normal evolution for the HF reaction (Scheme 26).

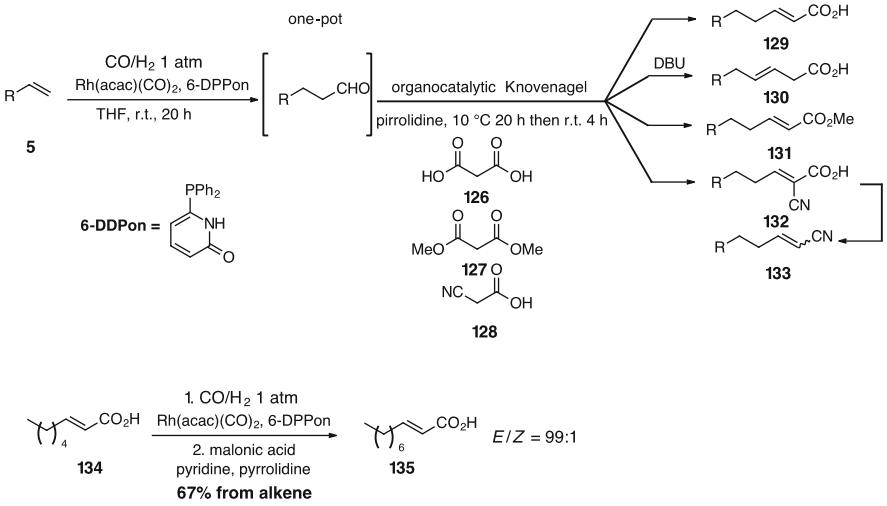
In 2007 Breit [65] and Eilbracht [66] independently reported the first domino HF, and cross aldol protocol catalyzed by Rh and proline catalysts respectively. In the first report the protocol is developed for the synthesis of enantioenriched diols starting from terminal alkene and small aldehydes. A crucial factor for the optimization of this protocol is the proper adjustment of the HF rate to the rate of proline-catalyzed aldol addition since accumulation of the donor aldehyde would generate by-products (i.e. homodimers). To achieve this goal a careful tuning of the Rh catalytic activity was needed, taking benefits from the application of different phosphine based ligands. Diols (**115**) can be obtained with good yields and stereoselectivities treating various terminal alkenes with aldehydes in the presence of $Rh(CO)_2acac$, 6-DDPon, and L-proline in DMF as the solvent at 15°C for 44 h under 20 atm of syngas in the presence of $NaBH_4$ (Scheme 27).

Reacting styrene or internal alkenes with ketones and L-proline at 40°C for 72 h under 40 atm of syngas, β-hydroxyketones were obtained with high stereo- and diastereoselectivities, $Rh(CO)_2acac$ again being the best catalyst in the presence of $P(OPh)_3$ (Scheme 28).

More recently, Breit and coworkers [67] use a developed room temperature/ambient pressure HF methodology as the first step in a decarboxylative organocatalyzed Knovenagel reaction, producing an efficient one-pot C3 homologation of terminal alkenes to (*E*)-α,β-unsaturated acids **129**, esters **131**, and nitriles **133**, (*E*)-β,γ-unsaturated acids **130**, and (*E*)-α-cyano acrylic acids **132**. Inspired from the fatty-acid biosynthesis an iterative two-carbon homologation of the (*E*)-α,β-unsaturated acid **134** is possible using a supramolecular catalytic system (Scheme 29).



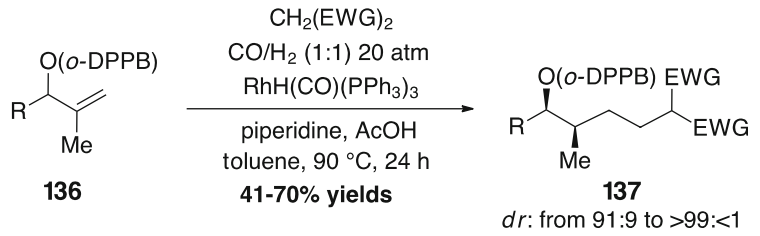
Scheme 28 Preparation of β-hydroxyketones



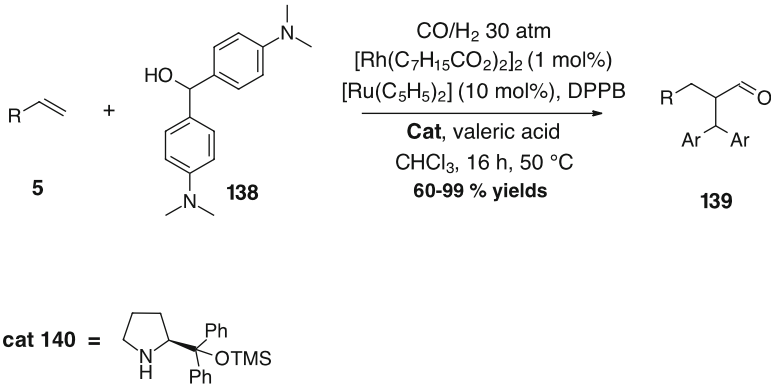
Scheme 29 HF domino with organocatalytic Knovenagel reaction

A similar protocol of HF/Knovenagel/hydrogenation reactions allows the regio- and stereoselective production of useful building blocks for polyketide synthesis (Scheme 30) [68].

A recent and very challenging application of HF in a domino process has been reported by Christmann, combining dual metal- and organo-catalysis to achieve α-substituted aldehydes with high enantiomeric excess [69]. In this protocol, a starting alkene is treated at 50°C for 16 h with Rh and Ru catalysts, with 1,4-bis (diphenylphosphino)-butane (DPPB) as the ligand at 30 atm of syngas, in the



Scheme 30 HF/Knovenagel/hydrogenation domino protocols



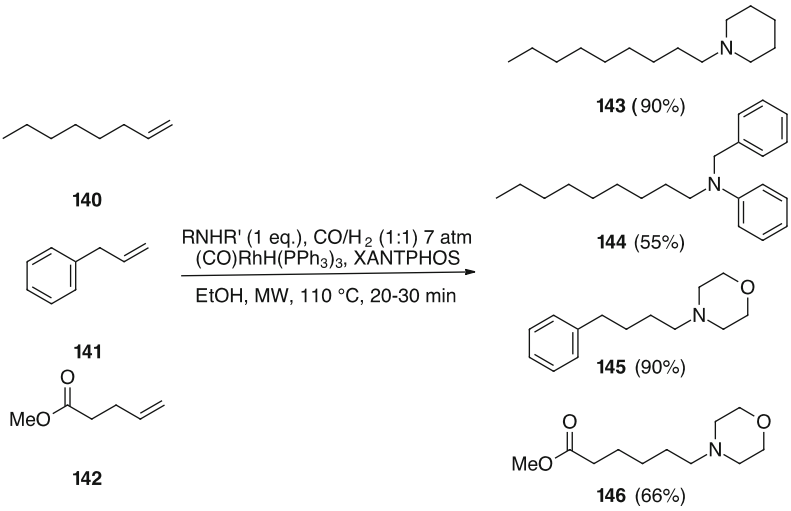
Scheme 31 Synthesis of α-substituted aldehydes

presence of valeric acid, a proper diaryl alcohol, and the organocatalyst **140** (Scheme 31). This transformation leads to the generation of two new C–C bonds with the formyl group still available for further transformations in the final products obtained in up to 92% ee using the Jørgensen–Hayashi organocatalyst.

These few contributions in domino HF and organocatalytic transformations represent an important starting point for the development of more sophisticated and versatile protocols able to generate new complex molecules in a stereocontrolled way, the use of heterogeneous metallo- and organocatalysts still remaining completely unexplored right now.

6 Microwave Assisted HF Domino Protocols

Despite the wide application of HF protocols in industry, this reaction is less useful on the laboratory scale, the main limitation being the need for high pressure resistant stainless steel autoclaves. Ordinary organic chemistry laboratories are usually not equipped with such apparatus, with consequent restrictions on HF application. Microwaves emerged in the last 20 years as an efficient energy source enabling

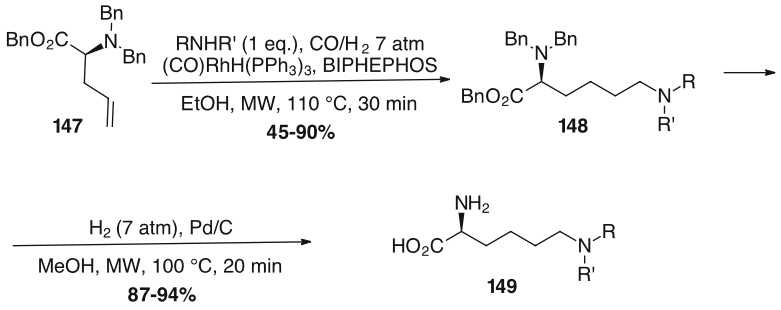


Scheme 32 Microwave-assisted HAM

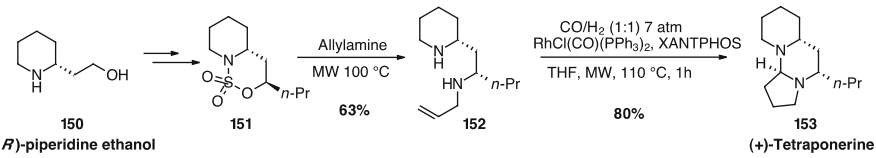
reactions to be run in shorter reaction times, and, sometimes, in milder reaction conditions, becoming nowadays a useful and common heating source in organic and medicinal chemistry laboratories. Microwave cavities are usually equipped with vessels able to resist high temperature, and pressures of maximum 20 atm, which leads to small autoclaves where the energy source for heating is microwave irradiation. Different protocols for the introduction of gas reagents inside a microwave cavity have recently been developed by different groups, demonstrating that hydrogenations [70, 71], carbonylations [72–74], and HF [75] can be easily run inside a microwave working in milder reaction conditions with respect to traditional heating, especially in terms of gas pressures and reaction temperatures [76]. Since the first report on microwave-assisted HF reaction [75], several application of this protocols to domino transformations have been reported, leading to efficient access to chemically and biologically interesting heterocycles and amines.

As previously reported, HAM is one of the most important domino processes involving HF. The main limitations of developed protocols are usually related to the excess of amines and expensive ligands or catalysts requested by traditional heating. Using microwave irradiation, HAM of terminal alkenes can be run in less than 30 min with stoichiometric amounts of secondary amines in EtOH using the cheapest $(PPh_3)_3RhCO(H)$, and XANTPHOS, and working at just under 7 atm of syngas (Scheme 32) [77].

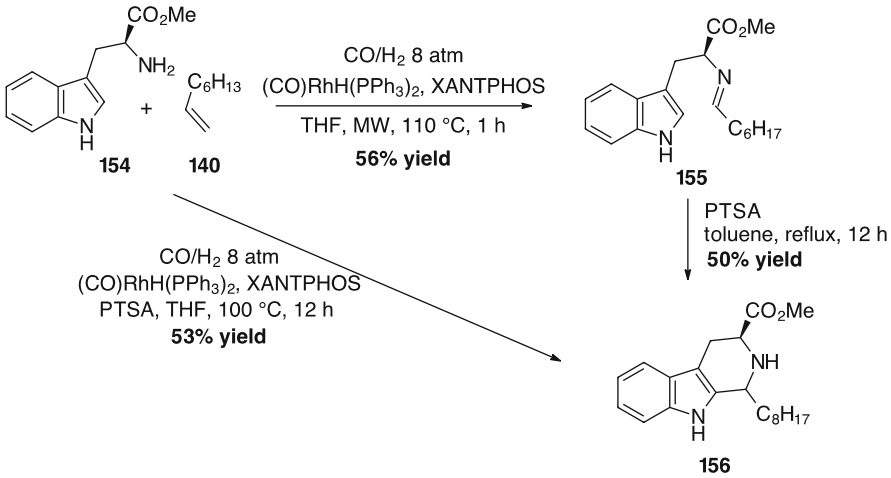
When primary amines were employed, the corresponding enamines are isolated in good yields, and the protocol proves to be applicable to the HAM of more complex substrates such as (*R*)-tris-benzyl allylglycine **147**. The different (basic) enantiomerically pure benzylated α-amino acids obtained in this way were deprotected in few minutes under MW irradiation with $Pd(OH)_2$ under H_2 atmosphere (Scheme 33) [77].



Scheme 33 Microwave-assisted HAM of (*R*)-tris-benzyl allylglycine and deprotection



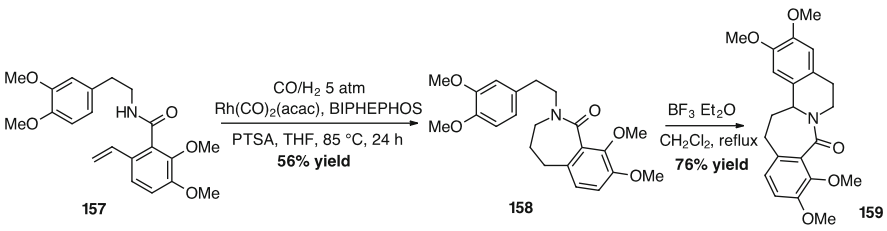
Scheme 34 Microwave-assisted CHC on the total synthesis of (+)-tetraponerine



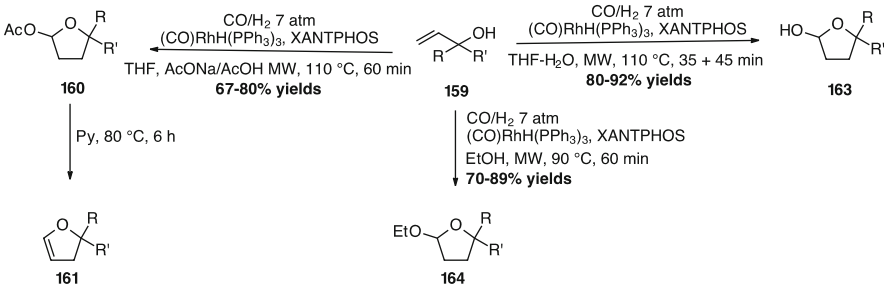
Scheme 35 Microwave-assisted domino HF and Pictect–Spengler reaction

Microwave assistance has been efficiently applied to a CHC protocol for the total synthesis of (+)-tetraponerine **153**, three new bonds and a new defined stereogenic centre being generated in a single reaction step. The CHC occurs in THF at just 7 atm of syngas, using $RhCl(CO)(PPh_3)_2$ and XANTPHOS, by irradiation with microwaves for 1 h (Scheme 34) [78].

It interesting to note that traditional thermal conditions appear to be crucial for the multi-component synthesis of **156**, as by microwaves irradiation only the corresponding imine has been isolated, any attempt to cyclise it failing under microwave-assisted conditions in the presence of different additives (Scheme 35)



Scheme 36 Domino HF and Pictect–Spengler reaction



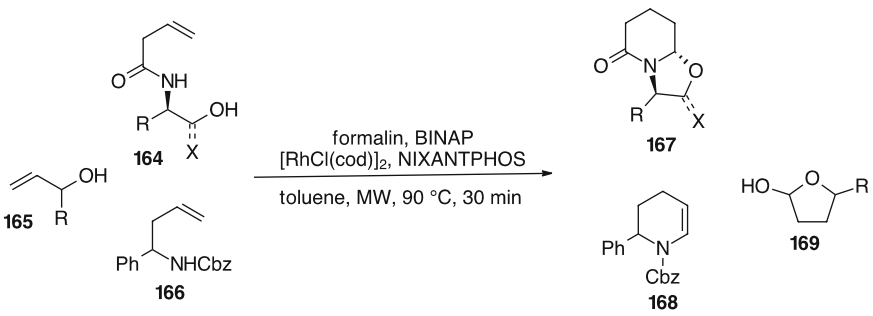
Scheme 37 Microwave-assisted domino HF in the presence of *O*-nucleophiles

[79]. This result suggests that the domino process depends on the success of the second reaction step. Although there are several reports describing a beneficial accelerating effect of MW on Pictect–Spengler reactions, conditions compatible with the MW-assisted HF process were not found by the authors.

The influence of the Pictect–Spengler reaction is revealed even in the preparation of 13-methylprotoberberine **159** where the HF of a suitable styryl derivative and acyliminum ion formation followed by Pictect–Spengler reaction occurred only in an autoclave (Scheme 36).

Taddei and Mann also reported the possibility of synthesizing lactol, and functionalized dihydro- and tetrahydrofuran derivatives by MW-assisted domino HF of unsaturated alcohols just using different solvents. The transformation occurs with both aromatic and aliphatic alcohols as well as with homoallylic alcohols, giving access in only 60 min to interesting intermediates in natural and bioactive products synthesis (Scheme 37).

One of the main limitations to the application in laboratory scale of HF protocols is represented by the use of syngas requested to run reactions to completion. Taddei recently reported a syngas-free MW-assisted HF domino protocol using formaldehyde as the CO/H_2 source [80]. An Rh(I) BINAP complex is used to catalyze the decomposition of formalin while Rh(I)NIXANTPHOS is effective in HF reaction. β,γ-Unsaturated amides **164** can be subject to domino HF by MW irradiation at 90°C for 30 min, giving oxazolidinones in good yields and regioselectivity (Scheme 38). This MW-assisted protocol seems to be effective on both nitrogen and oxygen nucleophiles, being efficiently applied even to the synthesis of lactols **169** starting from allyl or homoallyl alcohols **165**.



Scheme 38 MW-assisted HF domino protocol using formaldehyde as the syngas source

Although useful to simplify and speed up the traditional time consuming HF protocols, the use of MWs in domino HF is still limited by the sensitivity of the nucleophiles employed. While in the presence of oxygen nucleophiles MW-assisted domino HF protocols prove to be more efficient minimizing the classical by-products observed in autoclaves, when nitrogen nucleophiles are involved in the reaction cascade, MWs find limited application. MW dielectric heating seems to be incompatible with acyliminium ions chemistry as a partial degradative pathway operates during the irradiation. On the basis of the reports published so far, both MW irradiation and autoclave heating prove to be effective, useful and complementary for performing domino HF reactions. Nevertheless, MWs remain the first choice, as milder reaction conditions in terms of pressure, temperature and time are usually requested.

7 Conclusions

HF reaction can be considered as a very useful starting reaction in domino processes. After much effort, several domino protocols have been developed for the synthesis of variously decorated molecules as well as natural products and biologically relevant scaffolds. Using different catalysts and ligands, it is possible to tune the reactivity of properly designed substrates, obtaining interesting compounds with high regio- and diastereoselectivities. A key role in HF mediated domino transformations is played by the ligand, the CO/H_2 ratio and the solvent employed. The possibility of microwave assisted domino HF protocols, even in the presence of liquid, green sources of syngas as formalin, should produce a wider application of these transformations on a lab scale, giving fast access to interesting scaffolds for drug discovery and material sciences. In our opinion, a very important emerging area in this field remains the study of HF domino/organocatalytic processes, the few examples reported so far being very promising for the mild reaction conditions developed, and the good stereoselectivities observed.

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Rhodium-Catalyzed Hydroformylation in Fused Azapolycycles Synthesis

Roberta Settambolo

Abstract *N*-Heterocycles, including fused ones, have proven to be an important class of compounds since they possess biological and pharmacological activities themselves and serve as valuable intermediates for synthetic drug discovery. My interest in the synthesis of these compounds stems from studies dealing with the hydroformylation (*oxo*) of olefins. The dihydroindolizines and benzofused ones are easily generated via rhodium-catalyzed hydroformylation of *N*-allylpyrroles and indoles: the butanal intermediate undergoes an intramolecular cyclodehydration giving the final polycyclic compound. This chapter reports my results in the area of the conversions of *oxo* aldehydes with additional C,C-bond-forming reactions together with relevant work from other laboratories on additional C,N-bond-forming reactions, encountered in the field of Azapolycycles synthesis over the last 5 years or so. The intramolecular sequences for polycylization will be especially emphasized using rhodium complexes to effect these transformations, under both conventional and microwave heating.

Keywords Aza · Cyclodehydration · Heterocycles · Hydroformylation · Polycycles · Rhodium catalyst · Synthesis

Contents

R. Settambolo (✉)
CNR-ICCOM, UOS di Pisa, Dipartimento di Chimica e Chimica Industriale,
Università di Pisa, Via Risorgimento 35, 56126 Pisa, Italy
e-mail: roberta.settambolo@cnr.it

1 Introduction

N-Heterocycles, including fused ones, have proved to be an important class of compounds since they possess biological and pharmacological activities themselves and serve as valuable intermediates for synthetic drug discovery [1–3]. The synthesis of these compounds usually requires several steps when traditional methods are used [4].

Metal-assisted strategies have received increasing interest in heterocyclic chemistry in recent years [5–10]. In particular this approach offers great potential and diversity in carbon–carbon and carbon–heteroatom bond-formation processes, together with outstanding functional group tolerance and high stereoselectivity [11–13]. The hydroformylation reaction is a well known multireactant process for the introduction of a C_1 unit [14–16]. CO and H_2 are utilized in a metal-catalyzed process to introduce a formyl group into olefins (with linear and/or branched aldehydes formation), which allows subsequent skeleton expansion that may even be achieved in one-pot sequential transformations. As the hydroformylation reaction represents an industrially applicable methodology, extension to this technique towards multistep one-pot transformations is particularly appealing. The method has been evolving over the years as the complexes of transition metals other than cobalt, notably rhodium, platinum, and ruthenium, were found to catalyze the reaction [17–19]. While cobalt-based catalyst precursors constitute the best compromise between economic advantage and activity, the rhodium-based ones are in general much more active (even 10^5 times) and much more tolerant of the presence of other functional groups in the unsaturated substrates. The most frequently used catalyst system for homogeneous hydroformylation of alkenes is formed by mono- or bidentate phosphine ligands and a rhodium source, or a preformed complex of rhodium with these ligands [19–26]. Some results have been published concerning cooperative effects involving several metal centers for the rhodium catalyzed hydroformylation [27–29], as well as the use of rhodium without ancillary ligands [30, 31].

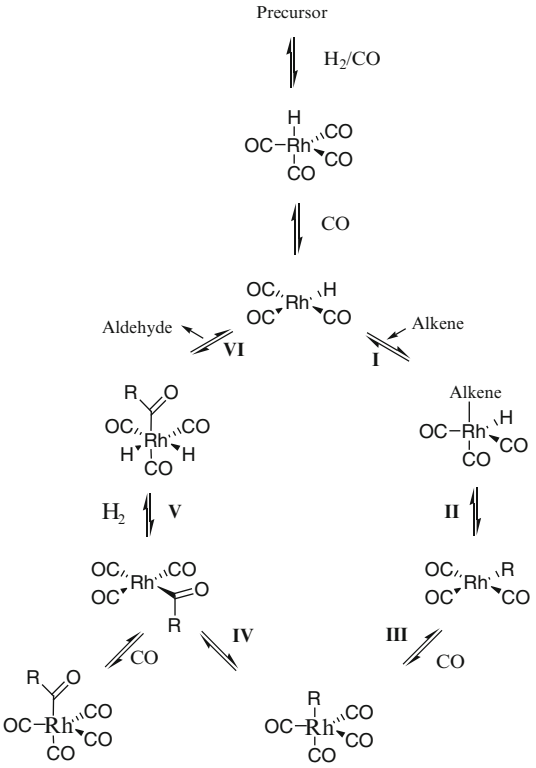


Fig. 1 Rhodium-catalyzed hydroformylation: generally accepted mechanism

A simplified scheme for the generally accepted mechanism for the hydroformylation processes catalyzed by unmodified rhodium precursors is reported in Fig. 1 and proposes the rhodium carbonyl hydride [$HRh(CO)_3$] as the catalytic active species of the reaction [32–38].

In the first stage (**I**) the alkene coordinates to a free site in the rhodium metal, giving rise to a π complex. In stage **II** the alkene inserts into the Rh–H bond, generating the alkyl–rhodium intermediates. These undergo the coordination of a fourth CO molecule to the metal center (stage **III**) and then give rise to the migratory insertion on a carbon monoxide in the *cis* position, leading to the formation of an acyl-rhodium species (stage **IV**). After the oxidative addition of H_2 on the latter intermediates a hexacoordinated Rh(III) complex was formed (stage **V**), which gives, via reductive elimination (stage **VI**), the final aldehydes and regenerates the catalytic species.

The main goal in the rhodium-catalyzed hydroformylation of unsaturated substrates concerns the control of the reaction regioselectivity, i.e., the branched aldehyde/linear aldehyde ratio.

The substrate structure as well as the experimental parameters can play a crucial role in determining the reaction regioselectivity.

Fig. 2 Branched and linear rhodium-alkyl intermediate

As far as the influence of the substrate nature is concerned, the hydroformylation of vinyl aromatic substrates i.e., styrene [39], vinylfurans [40], vinylthiophenes [41], vinylpyrrole [42, 43], and vinylpyridines [44–46] under mild temperature always provides a large predominance of the branched isomer over the linear one. Under the same conditions, alkenes with α hydrogens (i.e., linear 1-alkenes) give the two regioisomers in almost 1:1 molar ratio [47, 48]. The linear isomer largely predominates over the branched ones in the hydroformylation of 3-alkyl substituted allylalkenes (i.e., 3-methylbut-1-ene) [49].

In the case of vinylidenic substrates, bearing dialkyl, arylalkyl, diaryl groups, the linear isomer is almost exclusively produced [50, 51].

These results can be rationalized taking into account that under mild conditions the aldehydes' regioselectivity reflects the regioselectivity of the formation of the branched and linear rhodium-alkyl intermediate (Fig. 2); the same electronic and steric effects determining a prevalence of a single rhodium alkyl, will also favor the corresponding aldehyde.

As far as the influence of the reaction conditions on the regioselectivity is concerned, in the case of vinyl and vinylidenic alkenes, the amount of linear aldehydes increases by raising the reaction temperature and decreasing the CO and H_2 partial pressures. Indeed, this is a general trend in the hydroformylation of different substrates and constitutes a fundamental starting point for a rationalization of the influence of experimental parameters on the reaction selectivity [52].

Despite its industrial importance, metal-catalyzed hydroformylation has not found much application in organic synthesis. This situation has significantly improved during the past two decades. Of particular interest, for example, are the syntheses via hydroformylation of steroids [53–55], camphenes [56], and aminoacids [57–59]. One of the most important results, as far as the application of the rhodium catalyzed hydroformylation is concerned, is the synthesis of 2-arylpropanals. In this case the hydroformylation selectively gives the branched aldehydic isomer which is a useful precursor of 2-arylpropionic acids, a widespread class of non steroidal anti-inflammatory [60–62]. The hydroformylation of pyrrole derivatives is a result of the last few years' work, despite the huge amount of work concerning these interesting substrates included in bioactive molecules such as porphyrins rings and biliar pigments [63].

The hydroformylation of *N*-allyl-pyrroles and indoles, in the presence of unmodified $Rh_4(CO)_{12}$ as catalyst precursor, integrated into a domino reaction sequence, has been developed in our laboratories as a general approach to one nitrogen-containing dihydroindolizines and benzofused ones (see Fig. 3 for *N*-allyl pyrrole and indole) [64, 65]. This process type requires only a single setup of starting materials, reagents, and solvents and no isolation of intermediates is necessary. It quickly increases the complexity of a substrate and simultaneously makes economic use of the atoms and the functional groups available.

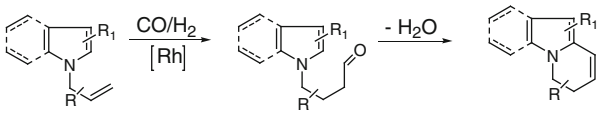


Fig. 3 Rhodium-catalyzed hydroformylation of N-allyl-pyrroles and indoles: formation of dihydroindolizines and benzofused ones

The indolizine building block at different degrees of unsaturation is a very common skeleton for many types of active natural and synthetic compounds. Among the fully hydrogenated substrates ([66, and references therein]; [67]), polyhydroxylated indolizidines mimic monosaccharides in their structure and ability to function as glycosidase inhibitors [68–71]; 5- or 3,5-alkylsubstituted indolizidines are also quite important biologically active derivatives [72–74]. They are used as intermediates in the synthesis of indolizines or indolizidines but they themselves also constitute target molecules, as illustrated by the extensive literature on 5,6,7,8-tetrahydroindolizines [75–78]. Among these, 7-aminotetrahydroindolizines are dopaminergic ligands [79] while 8-hydroxytetrahydroindolizines possess antiTNF and antithrombotic activities [80, 81]. Benzofused indolizines have attracted much attention as an analogue of the potent antitumor antibiotics mitomycins [82–86].

My primary purpose in writing this review is to highlight the importance of *oxo*-aldehyde intermediates for the synthesis of aza cycles via the interaction of the carbonyl-C carbon atom with nucleophiles as aromatic ring carbon atoms and nitrogen atoms in a single cyclization. Some examples of double cyclization are reported too.

As testified by the huge number of papers concerning this topic, the regio- and stereoselectivity of the hydroformylation reaction, and then its synthetic potentiality, can be modified by changing the reaction conditions and by using suitable ligands. On the other hand, a very important parameter which determines the ratio of aldehydic products of hydroformylation is the structure of the olefinic substrate itself, and this work is based on this feature.

2 Single Cyclization: Six-Membered Ring Formation via C,C-Bond of *oxo* Aldehydes

Hydroformylation creates a new carbon–carbon bond and moreover introduces the synthetically useful aldehyde function, which can be the starting point to further reactions. Thus the hydroformylation step can, in principle, be coupled with other steps in a one-pot intermolecular (and/or intramolecular) operation. When aldehydes obtained via hydroformylation undergo nucleophilic attack by activated aromatic systems they generate an additional C–C bond in a new cyclic structure. The case of both pyrrole and indole nucleus is taken into account.

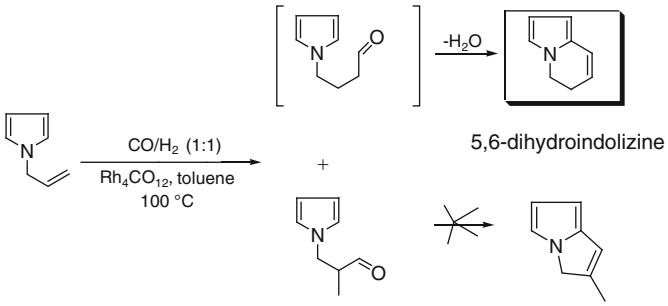


Fig. 4 Rhodium-catalyzed hydroformylation of N-allylpyrrole leads to 5,6-dihydroindolizine via an intramolecular cyclization which involves the linear aldehyde only

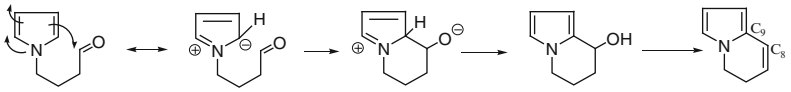


Fig. 5 Cyclization of 4-(pyrrol-1-yl)butanal to 5,6-dihydroindolizine via intramolecular electrophilic substitution in α-position of the pyrrole nucleus

2.1 From N*-Allylpyrroles: Formation of Dihydroindolizines and Tetrahydroindolizines*

Hydroformylation of *N*-allylpyrroles leads to 5,6-dihydroindolizines via a one-pot hydroformylation/cyclization/dehydration process (see Fig. 4 for *N*-allylpyrrole) [86, 87]. The cyclization step involves the linear aldehyde only and represents an intramolecular electrophilic aromatic substitution in the α-position of the pyrrole.

The process likely occurs via the formation of a bicyclic alcohol via C8–C9 bond construction: subsequent elimination of water gives the highly conjugated dihydroindolizine (Fig. 5).

The process occurs under conventional heating and in the presence of unmodified $Rh_4(CO)_{12}$ as catalyst precursor, characterized by easy availability (for the synthesis see [88, 89]) and easy handling [90]. Under hydroformylation conditions this species generates a rhodium-carbonyl hydride [$HRh(CO)_3$], which constitutes the catalytic active species of the reaction [32–38] (see Fig. 1).

The procedure was extended to optically active substrates [87] (Fig. 6). In this case unconverted starting material and the dihydroindolizines produced showed, at all conversions, almost the same enantiomeric excess, i.e., starting ee value (>92%). This result is unusual compared to that of other aromatic or aliphatic allylolefins because it indicates the absence of β-elimination to internal olefin during the process. As understood in the generally accepted mechanism of hydroformylation [31] (Fig. 1), the aldehydes' regioselectivity is strictly dependent on the alkyl-rhodium intermediates' regioselectivity. The allylpyrrole insertion into the Rh–H bond, which gives rise to the alkyl-metal intermediates L and B respectively along the pathway to

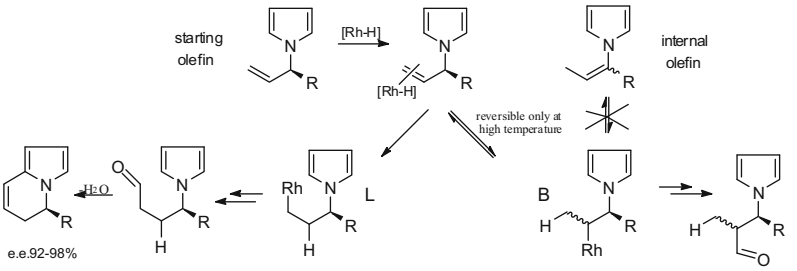


Fig. 6 Rhodium-catalyzed hydroformylation of (R)-3-alkyl-3-pyrrol-1-ylprop-1-enes: the β-elimination does not involve the chiral center

the linear or branched product aldehydes, can be a reversible or nonreversible step, especially depending on the temperature [87, 91].

At room temperature the formation of the alkyls is not reversible and the branched isomers prevail thanks to the electronic effect of the pyrrole ring [87]. In contrast, at high temperature, unlike the behavior observed with other olefins, e.g., allylbenzene [30, 92, 93], the branched alkyl-rhodium intermediate B undergoes a β-hydride elimination process, generating the starting olefin again and hence promoting a successive increase of the linear aldehyde. The β-elimination does not involve the chiral center: in fact an olefin which is the same as the starting one was generated but not the internal one (Fig. 6). The isomerized olefin was not observed in the crude reaction mixture at all conversions. The methynic hydrogen bonded to the carbon vicinal to the annular nitrogen does not give enough hydridic character to take part in β-hydride elimination, thanks to the electron-withdrawing heteroaromatic effect. In this case the sole hydroformylation is sufficient to rationalize the mechanistic iter of the reaction, and analogous deuterioformylation experiments, carried out in other reported cases [94–98], are not strictly necessary.

The aldehyde cannot be isolated under hydroformylation conditions: cyclization is faster than hydroformylation. The role of the rhodium or active rhodium-complexes in the cyclization process is not clear. The high reactivity of the butanal is likely due to the high nucleophilic character of the two pyrrole carbon atom with respect to the vicinal carbonyl carbon one. On the other hand, any rhodium species could accelerate the process, making the carbonyl carbon atom more electrophilic via oxygen coordination. It should be noted that this is a particular case of a domino process which starts with the interconversion of the rhodium-alkyl intermediates and carries on with the other steps of the cyclodehydration.

The dihydroindolizines are a useful starting material to tetrahydroindolizines. In fact, in the case of dihydroindolizine bearing an *n*-propyl group bonded to the C5-carbon atom (Fig. 7), when at complete conversion the gas mixture was removed from the crude hydroformylation product, H_2 (50 atm) was added, and the reaction vessel heated for a long time (12 h), the corresponding 5,6,7,8-tetrahydroindolizine was obtained (Fig. 7i): additional reduction of the pyrrole nucleus was never observed even by forcing the conditions (high pressure

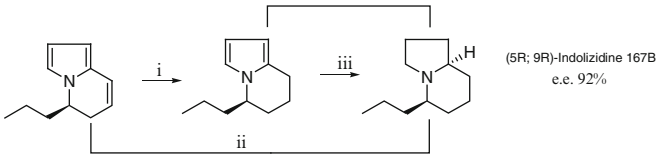


Fig. 7 Indolizines at different degree of unsaturation: i under H_2 50 atm, after CO and H_2 removal, heating for 12 h, 80% yield; ii H_2 10 atm, Rh/C (5%), r.t., 60 min, 64% yield; iii H_2 10 atm, Rh/C (5%), r.t. 45 min, 75% yield

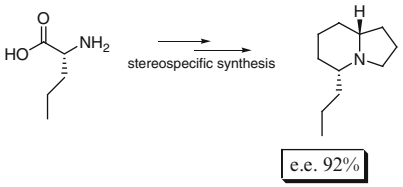


Fig. 8 (-)-Indolizidine 167 B from D-norvaline

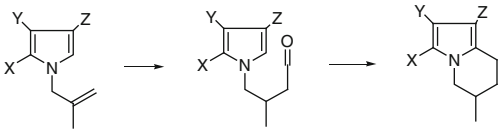


Fig. 9 5,6,7,8-Tetrahydroindolizines via rhodium-catalyzed hydroformylation of differently substituted N-(β-methallyl)pyrroles

and high temperature). This goal was successfully reached by treating the starting material with Rh on 5% carbon as catalyst precursor, under H_2 (10 atm), for 60 min (Fig. 7ii), or the tetrahydroindolizine intermediate under the same experimental conditions for 45 min respectively (Fig. 7iii). In both cases only the diastereomer corresponding to indolizidine 167B, characterized by C5 and C9 chiral centers with the same absolute configuration, was obtained, the reaction being completely stereoselective as evidenced by comparison with literature data [99] for the same isomer. Indolizidine 167B (Fig. 7), one of the simplest amphibian indolizidine alkaloids, was originally identified as a (5*R*,9*R*)-octahydroindolizine from the skin secretions of a frog belonging to the genus Dendrobates [100, 101], which acts as a noncompetitive blocker of neuromuscular transmission. Although the structure has been questioned [101], this alkaloid remains a target compound for many chemists throughout the world [102–107].

It should be noted that the global synthesis is completely stereospecific, with the final product having the same optical purity as the starting olefin (ee 92%).

This latter can easily be prepared from α-amino acids via a stereospecific synthesis [108]. The whole synthesis is stereocontrolled. Indeed, the chiral center in the starting amino acid is transferred into 5,6-dihydroindolizine moiety with complete stereochemical integrity and the new stereogenic center at the C9 carbon atom in the final indolizidine is generated in only one configuration (Fig. 8).

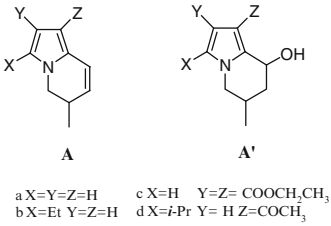


Fig. 10 Indolizine intermediates in the synthesis of tetrahydroindolizines via rhodium-catalyzed hydroformylation of N-(β-methallyl)pyrroles

5,6,7,8-Tetrahydroindolizines can also be prepared via a general domino protocol based on the rhodium-catalyzed hydroformylation of the differently substituted *N*-(β-methallyl)pyrroles [109] (Fig. 9). With respect to the above case where additional H_2 was added at complete substrate conversion, in this case the hydrogenation occurs under the applied *oxo* conditions (Fig. 9).

The sole aldehyde formed (consistent with the *oxo* behavior of vinylidenic olefins in general [50, 51, 86]) evolves to an indolizine skeleton via an in situ intramolecular cyclization on the α-pyrrole position by the carbonyl carbon atom followed by reduction of the six-membered ring. High temperature (140°C) and pressure (130 atm) values were necessary, i.e., no typical hydroformylation conditions [31].The nature of the substituent groups modulates the reaction times. With the electron-donating ethyl group on the 2-pyrrole position, the conversion time was 10 h. When two electron-withdrawing groups on the pyrrole ring were present, 72 h were necessary in order to achieve complete conversion. Intermediate values of reaction time were observed for other substrates depending on the groups' nature. The cyclization step conditions the global process rate. It is greater when no groups or an electron-donating group are present on the pyrrole ring: thus the availability of negative charge on the α pyrrole position results increased and the intramolecular attack from the aldehyde carbonyl group favoured. In this case no traces of pyrrolylbutanal were observed at all conversions but only 5,6-dihydroindolizine intermediates **Aa–b** (Fig. 10), deriving from an intramolecular cyclodehydration. The successive hydrogenation of the double bond into the six-membered ring gave rise to the corresponding tetrahydroindolizines. In the other cases, two different intermediates can be hypothesized (Fig. 10): the corresponding 5,6-dihydroindolizine **Ac–d**, as before, or the bicyclic alcohol **A′c–d** as in the case of the hydroformylation of 3-acetyl-1-allylpyrrole and 3-acetyl-1-β-methallylpyrrole (see later) [110]. An intermediate of this type has been found in the case of the pyrrole nucleus substituted with an isopropyl group in position two and an acetyl group in position four. **A′c–d** Could be favoured by an intramolecular hydrogen bond between the hydrogen of the hydroxyl group and the oxygenated substituent on the β-pyrrole position. In this light, the evolution to the final tetrahydroindolizine could occur from **A** via a double bond hydrogenation or from **A′** via a direct hydrogen removal of the hydroxyl group.

A particular case is constituted by the hydroformylation of 3-acetyl-*N*-allylpyrrole [111]. The reaction was carried out at high temperature (140°C) and low pressure (30 atm), experimental conditions favoring the linear isomer (regioisomeric molar

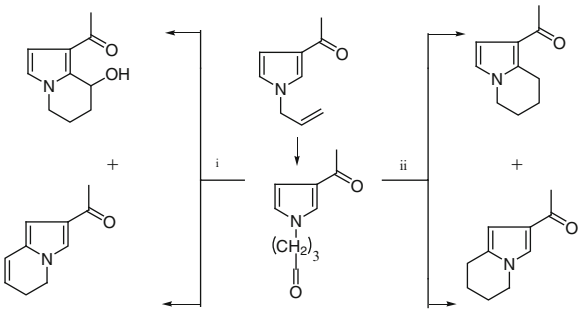


Fig. 11 Rhodium-catalyzed hydroformylation of 3-acetyl-N-allylpyrrole: different evolution of the pyrrolylbutanal formed depending on i) H_2 removal ii) presence of H_2 for long reaction times

ratio 85:15) as observed for other 1-allylpyrroles [87]. While the branched aldehyde, which was present in very small amounts, did not give cyclization products but only reduction to the corresponding alcohol, the butanal gives, for long reaction times ($\tau = 48$ h), two isomeric acetyl substituted 5,6,7,8-tetrahydroindolizines (1:1) (Fig. 11ii).

Interestingly, the aldehyde intermediate, in the presence only of CO and the rhodium catalyst, gives an alcoholic species in addition to a dihydroindolizine (Fig. 11i).

According to the previous report [87], the formation of 2-acetyl-5,6,7,8-tetrahydroindolizine is explainable by an electrophilic attack of the carbonyl group on the C5 pyrrole carbon atom via the corresponding dihydroindolizine, which was identified in the crude reaction mixture at partial conversion.

An analogous attack on pyrrole carbon atom C2 instead of C5 occurs for the formation of 1-acetyl-5,6,7,8-tetrahydroindolizine: in this case the corresponding bicyclic alcohol was found as a transient species. The latter does not undergo water elimination but is converted into the tetrahydroindolizine via a direct reduction of the hydroxyl group. Indeed, the corresponding dihydroindolizine has never been found in the crude reaction mixture. The bicyclic alcohol is likely to be stabilized by an intramolecular hydrogen bond between the hydroxylic hydrogen and the carbonyl oxygen atom with consequent formation of a tricyclic structure. This factor could be the driving force for the formation of this structure in an amount (1:1 molar ratio with respect to 2-acetyldihydroindolizine) that would not be expected on the basis of otherwise unfavorable steric and electronic effects. In accord with this structural hypothesis, the IR spectrum showed a band due to OH stretching at an unexpectedly low frequency (3,037 cm^{-1}). This value was independent of concentration (10^{-2}, 10^{-3}, 10^{-4} M solution in CCl_4) as expected for an intramolecular, rather than intermolecular, hydrogen bond. This is an alcohol which, unlike the other cases depicted here, is stable and can be handled at room temperature without decomposition.

The hydroformylation of the analogous 2-methyl-3-(3-acetylpyrrol-1-yl)prop-1-ene [110] constitutes an interesting example of 1,3-substrate induced diastereoselectivity.

This substrate is a prochiral compound and the butanal obtained is still a chiral compound: in particular the bicyclic alcohol which is formed is characterized by two chiral centers in the 1,3-position, respectively. ^{13}C and ^{1}H NMR spectra show only one resonance for every carbon and every proton, indicating that the

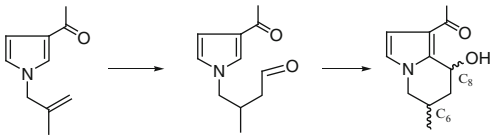


Fig. 12 Rhodium-catalyzed hydroformylation of 2-methyl-3-(3-acetylpyrrol-1-yl)prop-1-ene: formation of a bicyclic alcohol with two chiral centers

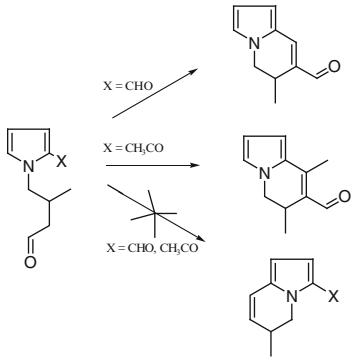


Fig. 13 Pyrrolylbutanals with an electron-withdrawing group on pyrrole 2-position undergo intramolecular aldol condensation instead of an intramolecular electrophilic substitution

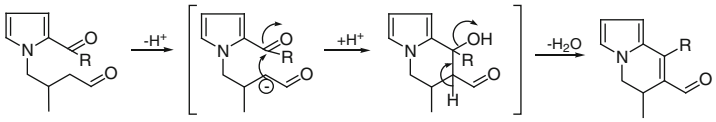


Fig. 14 Cyclization of a 4-(pyrrol-1-yl)butanal bearing an electron-withdrawing group on pyrrole 2-position to a 7-formyl-5,6-dihydroindolizine via intramolecular aldol condensation

intramolecular cyclization produces only one diastereomer, namely, that having chiral centers at carbon atoms C6 and C8 with the same relative configuration (6*S*,8*S*; 6*R*,8*R*) (Fig. 12).

The structure has been confirmed by DFT calculations at the B3LYP/6-31G* level (Gaussian 03 system of programs) [112], the geometry in the gas phase being fully relaxed. Quantum mechanical calculations indicate that the two diastereomers have the same thermodynamic stability; therefore, the complete diastereoselectivity of the reaction is likely to be due to the lower activation energy for the formation of the *R*,*R*, *S*,*S* diastereomer. This is one of the few cases reported in the literature of complete 1,3-asymmetric induction under hydroformylation conditions [15, 113].

The hydroformylation of 3-acetyl-1-allylpyrroles reported here constitutes an interesting extension of the reactivity of 1-allylpyrroles substituted with electron-withdrawing groups. Unlike the analogous 2-acetyl-1-β-metallylpyrrole [114], which undergoes intramolecular aldol condensation instead of intramolecular electrophilic substitution (Figs. 13 and 14), the presence of the acetyl group on the β-pyrrole

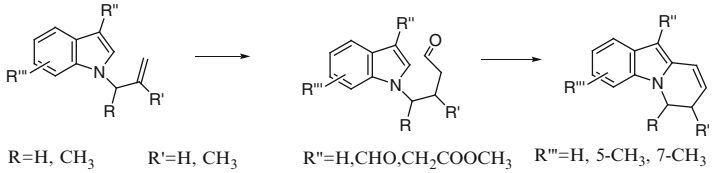


Fig. 15 Rhodium-catalyzed hydroformylation of differently substituted N-allylindoles to benzo-fused 5,6-dihydroindolizines

position makes the α-pyrrole positions still available for the electrophilic attack of the carbonyl moiety. Interestingly, cyclization is much slower than hydroformylation, thus allowing either the aldehydes or the corresponding cyclization products to be recovered as required.

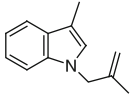
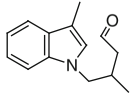
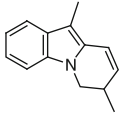
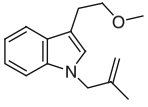
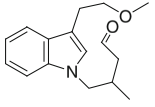
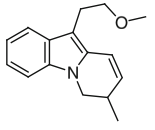
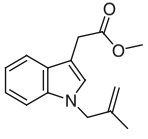
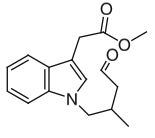
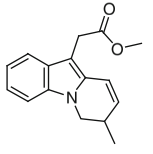
2.2 *From* N-*Allylindoles: Formation of Benzofused Dihydroindolizines*

The analogous 4-(indol-1-yl)butanals can be obtained via hydroformylation [115] of variously substituted *N*-allylindoles [116–119]. These aldehydes can either be isolated and characterized or undergo an in situ intramolecular cyclization on the indole 2-position to benzofused dihydroindolizines [65]: the crucial requirement is the presence of an electron-donating group on the indole 3-position (Fig. 15).

N-β-Methallylindoles were taken in account: the choice of this particular allylic chain allowed one to concentrate only on the reactivity of the 4-(indol-1-yl)butanal formed in the reaction, ignoring questions connected with regioselectivity. In fact with the simple *N*-β-methallylindole the linear aldehyde 4-(indol-1-yl)butanal was the sole product formed after 3 h, at 100°C and 100 atm. A similar behavior was observed when a methyl group was present on the indole 3-position, the linear aldehyde being exclusively formed (Table 1). No significant differences were found when the methyl group was on the indole 5- and 7-position respectively: in fact the corresponding aldehydes were obtained as exclusive products. The selectivity of the reaction was also independent of the nature of the substituent on the indole 3-position: with olefins bearing an electron-donating group ($R'' = CH_2CH_2OCH_3$ or CH_2COOCH_3) (Table 1) as well as in the case of olefins characterized by an electron-withdrawing group ($R'' = CHO$), the 4-indolylbutanals were chemoselectively formed.

The hydroformylation of the vinyl olefin with R = Me as substituent group under the same experimental conditions was faster, the conversion being complete after 0.5–1 h. However, in this case, the linear aldehyde 4-(indol-1-yl)pentanal was not the sole product, the branched 2-methyl-3-(indol-1-yl)butanal being formed in 40/60 molar ratio with the linear one. In the light of the above findings we can affirm that as far as the regio- and the chemo-selectivity is concerned the vinylidenic and vinyl indolyl olefins investigated behave similarly [31]. Interestingly, the resulting

Table 1 Hydroformylation[a] of *N*-β-metallylindoles to benzofused dihydroindolizines via 4-(indol-1-yl)butanals

Substrate	Yield (%)[b]	Hydroformylation time (h)	Hydroformylation products	Yield (%)[b]	Cyclization products	Yield (%)[b]	
						[c]	[d]
	78	3.5		82		80	75
	70	3		75		78	80
	75	3		80		81	–

[a] $Rh_4(CO)_{12}$ (100/1 = substrate/Rh), 100 atm total pressure (CO/H_2 = 1/1), 100°C, benzene as the solvent
[b] Yield of pure isolated product
[c] Pyridinium para-toluenesulfonate (5%) catalyzed, 2 h, benzene at reflux
[d] Rhodium-catalyzed, 40 h under N_2 atmosphere, after CO/H_2 gas mixture removal

indolylaldehydes were quite stable under hydroformylation conditions, their fate being quite different with respect to the parental 4-(pyrrol-1-yl)butanals: indeed the α-position of indole is less nucleophile than the α-position of pyrrole, and this determines a lower reactivity towards the carbonyl group for the formation of the six-membered ring.

When the CO/H_2 mixture was removed from the crude reaction mixture containing 3-methyl-4-(3-methylindol-1-yl)butanal and the reactor was pressurized with CO only, a decrease of the aldehyde was observed with a simultaneous formation of the corresponding benzofused dihydroindolizine (Table 1). After 40 h, the latter was the sole product present in the crude reaction mixture. Under the same experimental conditions, the analogous olefin containing the methoxyethyl group on the indole 3-position, gave the corresponding dihydroindolizine (Table 1). In contrast, cyclodehydration of aldehyde [1-(2-methyl-4-*oxo*-butyl)-1*H*-indol-3-yl]acetic acid methyl ester does not occur. Neither does aldehyde 3-methyl-4-(indol-1-yl)butanal undergo this transformation and the result is the same regardless of the position of the methyl group on the alkyl chain bonded to the nitrogen atom: indeed aldehyde with a methyl substituent group on the carbon atom near to the nitrogen one also remains intact. Olefins 2-methyl-3-(5-methylindol-1-yl)propene and 2-methyl-3-(7-methylindol-1-yl)propene behave in the same manner: the corresponding aldehydes were recovered unchanged after heating for a long time. Aldehyde substituted with a formyl group on position 3 of the indole moiety also does not cyclize. The above data suggest that the presence of a group activating at least as much as a methyl, which contemporarily blocks the most nucleophilic site of the ring, should be present on the indole 3-position in order to promote indolizine formation; in this way the less nucleophilic indole 2-position becomes capable of reacting with the aldehyde carbonyl carbon atom to give a new six-membered ring. Subsequent dehydration gives the highly conjugated benzofused dihydroindolizine system. In any case, the intramolecular electrophilic substitution can still be promoted under acid catalysis, in particular by heating for about 2 h under reflux in diluted benzene with a catalytic quantity (5%) of pyridinium para-toluenesulfonate (Table 1). Maybe the steric hindrance exerted by the substituent in position 3 plays a crucial role, inhibiting the intramolecular cyclization under rhodium catalyzed conditions. Analogously, pyridinium para-toluenesulfonate promotes the cyclodehydration of 3-methyl-4-(3-methylindol-1-yl)butanal and the aldehyde bearing the methylethoxy group (Table 1). A similar cyclization attempt on the other aldehydes was unsuccessful: it was neither possible to recover any starting material nor isolate any product. Interestingly, in spite of the darkening of the solution, most of the starting aldehyde was recovered by simple filtration on celite. Thus the presence of an electron-withdrawing group on the indole 3-position is crucial for the survival of indolylbutanals under the mild acidic conditions; otherwise intermolecular reactions take place probably on the more favoured β-position of the indolyl units [120].

Due to the pharmaceutical importance of mitomycins, the synthesis of mitomycins and mitomycin-like compounds, as the reported structures, has attracted much attention [82, 83, 85]. The benzofused indolizine skeleton is

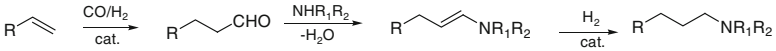


Fig. 16 Hydroaminomethylation reaction

known and different cyclizations have been used for the formation of the six-membered ring starting from an indole derivative. Indeed, the example reported here constitutes the first case of the use of hydroformylation as the key step.

Hydroformylation of N-Allyl-Pyrroles and/or Indoles with $Rh_4(CO)_{12}$: Typical Procedure

A solution of the proper *N*-allyl-pyrrole and/or indoles (1–2 mmol) and of $Rh_4(CO)_{12}$ (in the molar ratio ranging from 250/1 to 100/1) in toluene (5–6 mL) is introduced by suction into an evacuated 25-mL stainless steel autoclave under magnetic stirring. This one is filled with carbon monoxide up to the desired pressure and heated up to the required temperature (20–140°C).

After 15 min hydrogen is introduced giving the proper final pressure [CO/H_2 = 30–120 atm (1/1)]. When the reaction started the drop in pressure was compensated by injection of a carbon monoxide–hydrogen mixture (1:1) from a high pressure container. When the gas absorption reached the value corresponding to the desired conversion, the reaction vessel was rapidly cooled, the reaction mixture was siphoned out, and GLC was used to determine the isomeric composition. The degree of conversion was measured by GLC by using acetophenone as internal standard. At complete conversion of the starting olefin, the residual reaction gases are evacuated and the crude reaction mixture directly taken out of the open autoclave for further manipulation.

3 Single Cyclization: Six-/Seven-Membered Ring Formation via C,N-Bond of *oxo* Aldehydes

When an *oxo* aldehyde reacts with a nitrogen nucleophile the structures of the product depend on the nature of nucleophiles present in the reaction moiety. With primary amines, imines are formed, whereas the presence of secondary amines leads to iminium ions (or enamines).

The hydroaminomethylation reaction (Fig. 16) is an elegant approach to the synthesis of secondary and tertiary amines from olefins originally discovered by Reppe et al. [121] in the early 1950s.

It is a well-known protocol, and its mechanism has been previously established ([15]. For reviews see [122, 123]). The intramolecular version, with the amino group bonded to the olefin submitted under hydroformylation, is a powerful synthetic instrument to aza heterocycles [15, 16, 19, 113, 124–127].

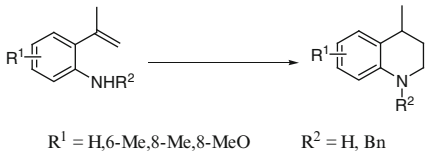


Fig. 17 Intramolecular hydroaminomethylation of isopropenylanilines: preparation of tetrahydroquinolines

Here the rhodium catalyst is involved in both steps, the hydroformylation of an olefin as well as the hydrogenation of the imine or enamine resulting from a condensation of the *oxo*-aldehyde with the amine. As previously depicted with *N*-β-metallylpyrroles, in this case the use of vinylidenic substrates assures the exclusive formation of the linear aldehydes, thus improving the reaction chemoselectivity.

3.1 On Isopropenylanilines: Formation of Tetrahydroquinolines

Intramolecular hydroaminomethylation tandem reaction was successfully used by Alper et al. in the development of a practical method for the construction of tetrahydroquinolines from 2-(prop-1-en-2-yl)anilines differently substituted at the nitrogen and in the aromatic ring. 1,2,3,4-Tetrahydroquinolines were obtained in good yields and in high chemo- and regioselectivity (Fig. 17) [128].

The reactions were performed on a 1-mmol scale at 120°C, in toluene (2 mL) for 48 h under 1,000 psi CO/H_2 (7:3) using ionic rhodium(I) diamine complexes (composed of an anionic rhodium center containing chloride ligand, and a cationic rhodium center coordinated by a diamine ligand) (5.0 mol%) as the catalyst. This system, as $Rh_4(CO)_{12}$ employed in the synthesis of indolizines (see above), is able to catalyze the hydroformylation reaction under mild reaction conditions in excellent activity and regioselectivity and can be manipulated without degasing the solvent prior to charging the autoclave, simplifying the manipulation.

Tetrahydroquinolines are the subject of high interest in the fields of natural products and medicinal chemistry [129–131]. They are useful for the preparation of pharmaceuticals and agrochemicals, as well as in materials science [132, and references cited therein]. In the past the most convenient and direct route to tetrahydroquinolines was the partial hydrogenation of quinolines [133–135], but the preparation of starting material often requires harsh conditions such as high temperatures and/or strongly acidic media.

3.2 On 2-(Prop-1-en-2-yl)benzylamines: Preparation of Benzazepines

When the substrates were isopropenylamines, 2,3,4,5-tetrahydro-1*H*-2-benzazepines were isolated in excellent yields (>91%) [136] (Fig. 18) under experimental conditions similar to those given above.

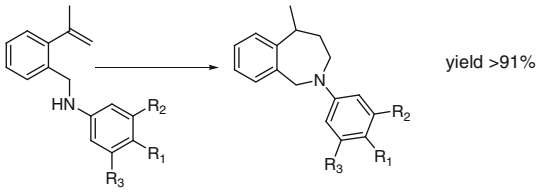


Fig. 18 Intramolecular hydroaminomethylation of isopropenylamines: preparation of benzazepines

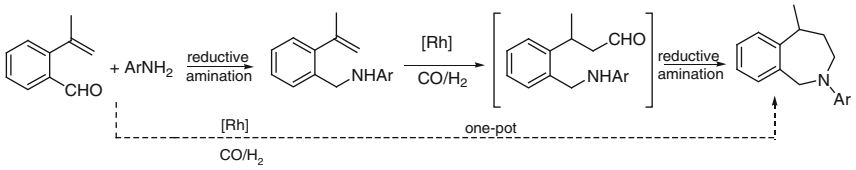


Fig. 19 Benzazepines via one-pot three-component multistep approach (reductive amination/hydroformylation/reductive amination)

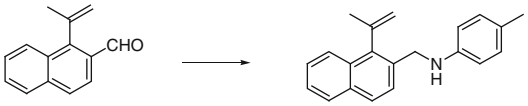


Fig. 20 Evidence for reductive amination and not hydroformylation as first stage in the preparation of benzazepines

The starting substrates were prepared from the corresponding aldehyde according to a standard procedure (for the preparation of the intermediate imines the procedure was adapted from [137]). They can also be prepared under hydroformylation conditions giving the final product in a three-component one-pot, catalytic approach (Fig. 19).

The route begins and ends with reductive amination and begins too. This iter is suggested from the case reported in Fig. 20, which only formed the final amine in 90% yield. The reaction stopped after the first reductive amination, and the hydroformylation could not take place, probably due to steric hindrance.

The 2-benzazepine moiety constitutes the core of a number of pharmacologically important compounds [1]. Several members of this class have exhibited hypotensive, analgesic, anticonvulsant, and antiarrhythmic activities, and have also proved to be useful for the treatment of mental disorders and hypoxia [138–140].

The synthetic protocol tolerates 2-(prop-1-en-2-yl)benzaldehyde and anilines of diverse nature affording different 2,3,4,5-tetrahydro-1*H*-2-benzazepines in excellent yield.

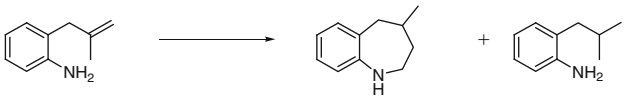


Fig. 21 Intramolecular hydroaminomethylation of 2-(methallyl)aniline: exclusive formation of a seven-membered ring

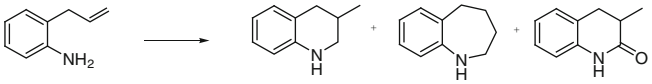


Fig. 22 Intramolecular hydroaminomethylation of 2-allylaniline: formation of a mixture of six- and seven-membered ring

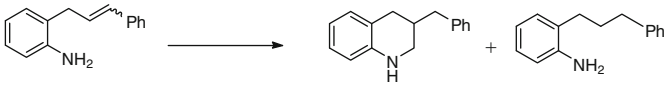


Fig. 23 Intramolecular hydroaminomethylation of 2-(3-phenyl-2-butenyl)aniline: formation of 3-benzyl-1,2,3,4-tetrahydroquinoline in up to 60% yield (formation of a six-membered ring)

3.3 On Allylanilines: Formation of Tetrahydroquinolines and/or Benzazepines

Allylanilines give good yields of aza heterocyclic compounds under hydroformylation conditions [141].

As previously observed with other vinylidenic substrates, the reaction applied to 2-(methallyl)aniline (Fig. 21) resulted in the exclusive formation of a seven-membered cycle coming from the sole linear aldehyde formed.

In most cases the reaction was not chemoselective. The simple 2-allylaniline gives three products (Fig. 22), a mixture of six- and seven-membered ring hydroaminomethylation products, and the six-membered ring cyclocarbonylation product in a ratio 49:8:24 in yield. The corresponding seven-membered cyclocarbonylation product was not formed.

Various attempts to modify experimental conditions (partial pressure of CO and/or H_2, steric demand of diamine complex, solvent nature, etc.) were carried out in order to improve the chemoselectivity. The best result was obtained with 2-(3-phenyl-2-butenyl)aniline [aniline (1.0 mmol), ionic *N*,*N*,*N*′,*N*′-tetramethylethylenediamine rhodium(I) complex (0.05 mmol), THF, $CO/H_2 = 100/700$ (psi)] giving 3-benzyl-1,2,3,4-tetrahydroquinoline in up to 60% yield with no seven-membered product being formed (Fig. 23).

The presence of the hydrogenation product was detected (28%). The hydrogenation might complete with hydroaminomethylation under high partial pressure of H_2 due to steric hindrance of the double bond. The hydrogenation product was suppressed under increased relative CO pressure to H_2 [$CO/H_2 = 300/700$ (psi)], the yield of tetrahydroquinoline improving substantially up to 69%.

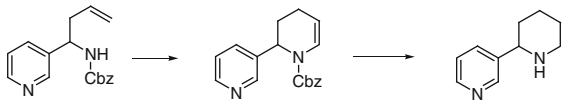


Fig. 24 Synthesis of (±)-anabasine via final hydrogenation of enamide intermediate

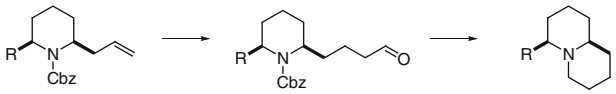


Fig. 25 Quinolizidines via rhodium-catalyzed hydroformylation of piperidines to the corresponding linear aldehyde followed by deprotection/reductive amination sequence

3.4 On Homoallylpiperidines: Formation of Quinolizidines

Homoallylamines give good yields of aza heterocyclic compounds if experimental conditions for a linear hydroformylation are applied and a useful cyclization with the amino group conveniently occurs.

An example in this field is constituted by homoallylamine, reported in Fig. 24, giving the final enamide in excellent yield (81%). In order to increase the selectivity into linear aldehyde a sterically demanding bidentate ligands was necessary: in this case $Rh(CO)_2(acac)$ (0.5 mol%) and the biphosphite BIPHEPHOS [23, 142] (1 mol%) was used as the catalytic system [143]. The hydroformylation proceeded in the presence of pyridinium *p*-toluenesulfonate with a very good catalyst-based regiocontrol. Then the enamide was hydrogenated with Pearlman's catalyst [H_2 5 bar, $Pd(OH)_2/C$ (10%), MeOH, rt, 24 h], promoting a clean tandem piperidine deprotection/double bond reduction to (±)-anabasine (34% overall for three steps).

When the amino-alkene is a piperidine derivative, various quinolizidines can be prepared (Fig. 25) [143].

The piperidines were homologated to the corresponding linear aldehyde by hydroformylation under standard conditions. No intramolecular cyclization occurs in this case. Successively the aldehydes were submitted to the deprotection/reductive amination sequence to give the corresponding racemic quinolizidines.

4 Double Cyclization

After the first cyclization, if a nucleophile is present in the substrate, an additional intramolecular reaction takes place in a domino multicomponent process. In this way more complex molecular architectures can be formed.

The reactivity of the second nucleophile is decisive for the outcome of the domino sequence. With aromatic C-nucleophiles, a cyclization often followed by rearomatization occurs; with a π-nucleophile (as an allylsilane) the ring closure

Fig. 26 (+)-tetraponerine T-3

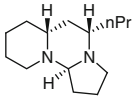
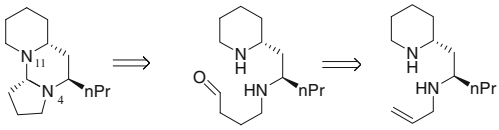


Fig. 27 Retrosynthesis of tetraponerine



generates a carbocation that evolves by elimination. With N-nucleophiles, attacks on an iminium ion (or enamines) and/or an acyliminium ion take place.

4.1 Six/Six-Membered Rings Formation via Additional C–N Bond

4.1.1 On an Allyldiamine

It is the case of the preparation of (+)-tetraponerine T-3 (Fig. 26) [143].

This compound has been prepared starting from the proper allyldiamine according to the retrosynthetic sequence reported in Fig. 27: the hydroformylation introduces a formyl group in a linear aldehyde intermediate which promotes the concomitant formation of a fused ring system by reductive cyclohydrocarbonylation (CHC) reaction on the two nitrogen atoms N-4 and N-11.

The diamine decomposing under conventional heating, the process was carried out under microwave (MW) conditions, at 100°C and H_2/CO (1:1) 7 bar pressure, in the presence of $RhCl(CO)(PPh_3)_2$ catalyst and the biphosphane XANTPHOS [23, 142].

The use of microwaves to heat organic reactions has attracted considerable attention during the last two decades [144–147]. This technique requires reduced reaction times, minimizes the formation of by-products, and thereby improves yields and purity. It uses reactors which can be considered as small autoclaves, adjusted to run reactions with gaseous reagents (they have been designed to withstand the high pressure internally generated by the solvent) and then useful for *oxo* process too. With respect to the classical hydroformylation process in autoclave, the reaction time and temperature were considerably reduced, and improvements in the selectivity were observed in some cases [148–150]. With this technique hydroformylation becomes a very economic process because the experimental runs can be carried out in small flasks, the amount of H_2 and CO wasted at the end of the reaction being reduced to a minimum.

These conditions in general simplify the *oxo* process but, as reported above, are often limited by the sensitivity to the nucleophiles.

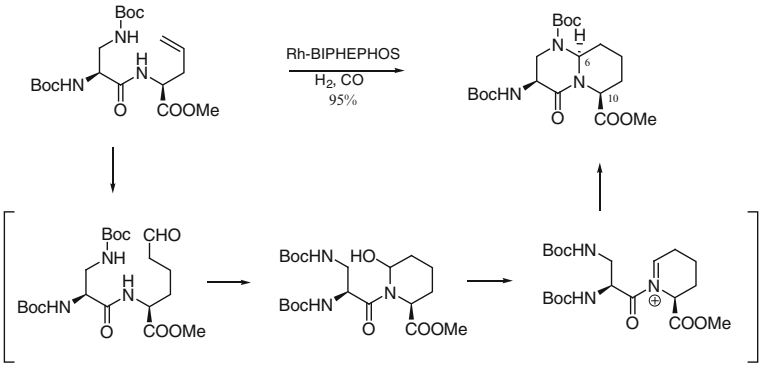


Fig. 28 An example of consecutive double cyclization highly diastereoselective

Hydroformylation Under Microwaves Conditions: Typical Experiment

The starting alkene (0.64 mmol) was dissolved in toluene (4 mL). $(Ph_3P)_3Rh(CO)H$ (0.013 mmol), XANTPHOS (0.05 mmol) and [bmim][BF_4] (187 μL) were added [140, 145, 148].

The solution obtained was submitted to pressurized syngas at 40 psi (2.7 atm) and heated for 4 min at 110°C by microwave irradiation at 150 W. The flask was cooled and the internal gas released. Et_2O was added to the reaction mixture and washed twice with H_2O; the organic layers were washed with brine and dried on dry Na_2SO_4. After filtration and evaporation in vacuo the residue was subjected to products isolation.

4.1.2 On Unsaturated Dipeptide Derivatives

The double cyclization applied to the title substrates gave 1-azabicyclo[*x*.*y*.0]alkane amino acid derivatives and their congeners [151].

The process involves (1) a selective hydroformylation of the terminal alkene moiety to the corresponding linear aldehyde, (2) intramolecular condensation to form cyclic *N*-acyliminium key intermediate, and (3) a second cyclization through intramolecular nucleophilic addition of a heteroatom nucleophile to the cyclic *N*-acyliminium moiety to afford the corresponding 1-azabicyclo[*x*.*y*.0] system. In Fig. 28 is shown the case of the synthesis of (3*S*,6*S*,10*S*)-1,5-diaza-3- *tert*-butoxycarbonylamino-5- *tert*-butoxycarbonyl-10-methoxycarbonyl-2-oxobicyclo [4.4.0] decane in which the second nucleophile is a nitrogen atom.

It involves a one-pot Rh-catalyzed cyclohydrocarbonylation (CHC) that induces a cascade double cyclization process.

The process starts with an extremely regioselective hydroformylation giving the linear aldehyde exclusively and continues with the first cyclization to yield the corresponding hemiamidal. After the conversion of hemiamidal to *N*-acyliminium

ion, the second cyclization through addition of an intramolecular nucleophile nitrogen-based takes place to give the final azabicyclic product.

The cyclohydrocarbonylation was carried out by using Rh(acac)$(CO)_2$–BIPHEPHOS catalyst at 60°C and 4 atm of H_2 and CO (1:1) in toluene and a catalytic amount (10%) of PTSA.

The chiral carbon in the C-10 position is the stereogenic center for the second cyclization that determines the stereochemistry at the bridgehead carbon (C-6). The nature of the substituent at the C-10 position exerts a critical effect: in the case considered a carbamate group is the internal nucleophile trapping the *N*-acyliminium intermediate. Thus, the reaction of starting dipeptide (*S*,*S*), bearing a β-aminoalanine moiety, proceeded efficiently under the standard conditions to give the final (3*S*, 6*S*, 10*S*) structure as a single product in 95% yield (Fig. 28).

This method has been successfully applied to the syntheses of 1-azabicyclo [4.4.0], -[5.4.0], and -[4.3.0] systems.

Azabicyclo[*x*.*y*.0]alkane amino acids [152, 153] are of great interest as building blocks in the synthesis of peptidomimetics [154–156] and as an instrument to investigate the peptide structure–activity relationships [157, 158].

Cyclohydrocarbonylation: Typical Procedure

Into a 10-mL round-bottomed reaction flask Rh(acac)$(CO)_2$ (0.0073 mmol) and BIPHEPHOS (0.0148 mmol) were placed. Nitrogen was introduced instead of the previous atmosphere together with degassed toluene (1.0 mL). The solution obtained was stirred until it became homogeneous. The catalyst solution was transferred, via syringe, to a 25-mL reaction flask containing the dipeptide substrate (0.363 mmol) and PTSA (0.036 mmol). The reaction flask was placed in a 300-mL stainless steel autoclave. The autoclave was flushed several times with CO, filled with 2 atm of CO, followed by 2 atm of H_2, and heated at 60°C with stirring for 20–24 h. Then the autoclave was cooled to room temperature and gases were slowly released. The reaction mixture was then concentrated under reduced pressure to give a viscous oil which was handled for products isolation.

5 Double Cyclization: Six/Six- and/or Six/Five-Membered Rings Formation via Additional C–C Bond

Electron-rich aromatic moieties can act as C-intramolecular nucleophiles in the second cyclization. Two examples are reported using *N*-allylic amides of arylacetic acids and vinylacetamides as starting substrates (Fig. 29).

The starting substrate is characterized by a terminal double bond and a nucleophile linked through an amide group working itself as an additional nucleophile. Indeed, upon hydroformylation, the amide NH will react with the newly formed aldehyde,

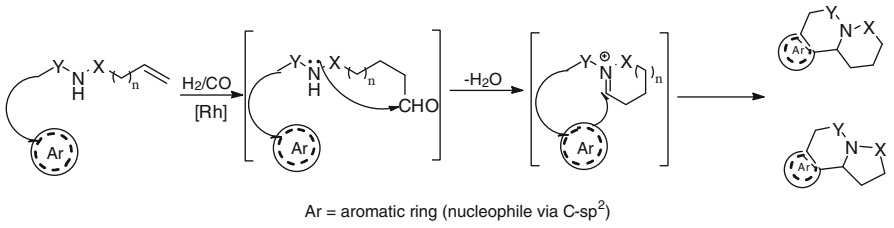


Fig. 29 Electron-rich aromatic moieties as C-intramolecular nucleophiles in the second cyclization

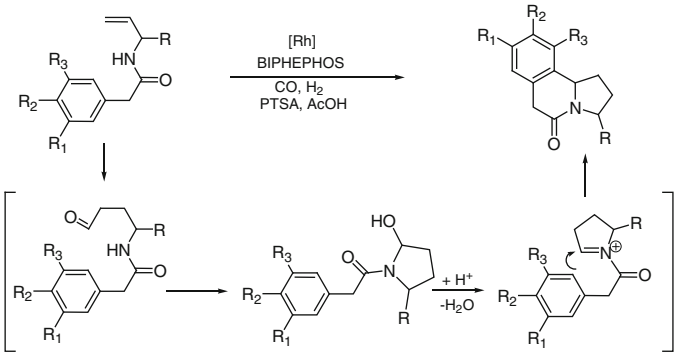


Fig. 30 An example of double cyclization via rhodium-catalyzed hydroformylation of N-allylic amide of phenylacetic acid

giving a highly activated *N*-acyliminium ion. Then a second nucleophilic attack completes the sequence of the domino CHC and generates the final polycyclic products. The structure of the products obtained with this strategy will be subordinated to the nature of the three reactive centers (vinyl, amide, and nucleophile) and their relative locations. Allylsilanes also (see 5.3) can act as nucleophiles with an acyliminium ion thanks their C-sp^2.

5.1 On N*-Allylic Amides of Arylacetic Acids*

This domino process [159] (Fig. 30) commences with a linear selective hydroformylation of *N*-allylic amide of phenylacetic acid to yield the corresponding aldehyde, which undergoes, in the presence of an acid, the first cyclization to form a hemiaminal. The latter undergoes a dehydration generating an *N*-acyliminium ion. Then a second cyclization occurs in which an electron-rich

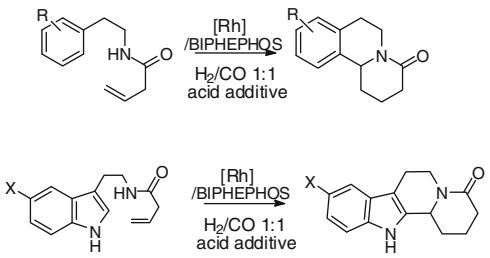


Fig. 31 Examples of double cyclization via rhodium-catalyzed hydroformylation of vinylacetamides

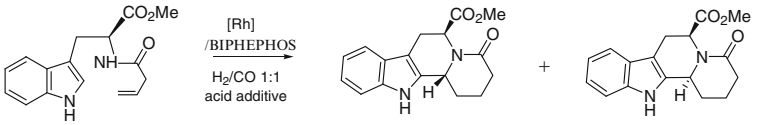


Fig. 32 Example of double cyclization via rhodium-catalyzed hydroformylation of a tryptophan methyl ester derivative: diastereoselectivity is modulated by acid additive

aromatic plays the role of the nucleophile to afford the third ring. This process is applicable to *N*-allylamide of indole-3-acetic acid with analogous result.

These cyclohydrocyclizations were carried out in the presence of catalytic amounts of Rh/BIPHEPHOS complex and PTSA under CO and H_2. Although this catalyst is able to favor linear aldehyde [23, 24, 160], the formation of a low amount of branched aldehyde was observed. This result may be due to a partial amide-directed chelation control [161].

5.2 On Vinylacetamides

When the starting materials were the phenethylamine derivatives and indole derivatives as shown in Fig. 31 the corresponding polycyclic adducts were isolated in good to very good yields [162].

They result from linear hydroformylation and subsequent quenching of the transient *N*-acyliminium with the electron-rich aromatic ring. Depending on the substrates, various quantities of acid additives were necessary to obtain good yields. The resulting domino CHC/Pictet–Spengler [163, 164] reaction works well with Brønsted or Lewis acid (PTSA, $BF_3{\cdot}Et_2O$) and provides benzo[*a*]quinolizidine-type products in very good yields (>67%) and good diastereoselectivity. With indole derivatives, $BF_3{\cdot}Et_2O$ gave better results and indoloquinolizidines were obtained with good (>73%) yields. With tryptophan methyl ester derivatives (Fig. 32) the nature of the acid additive has a great influence on the stereoselectivity of the reaction. Indeed, in the presence of PTSA, a mixture of two diastereoisomeric adducts, separable by chromatography, was obtained with 95% yield and a good diastereoselectivity (88:12: the configuration of the major diastereomer was

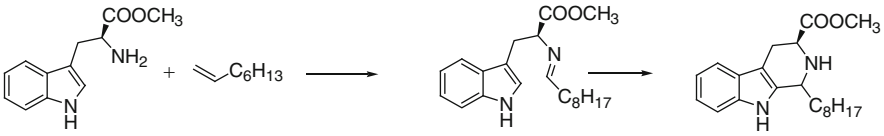


Fig. 33 Rhodium-catalyzed hydroformylation of a mixture of tryptophan methyl ester and oct-1-ene under MW heating: no cyclization occurs, the corresponding imine being only formed

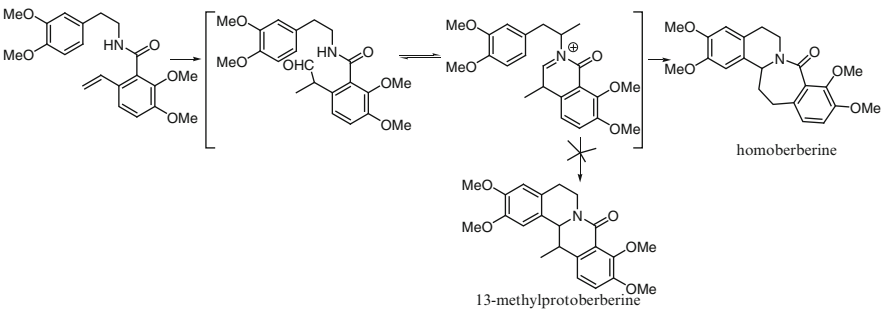


Fig. 34 Synthesis of homoberberine instead of 13-methylprotoberberine expected

confirmed by X-ray diffraction analysis), whereas, with $BF_3{\cdot}Et_2O$, a 1:1 mixture of the two diastereomers was obtained.

Under MW conditions this reaction is hampered and only an isomer of the starting material was found at the end of the reaction.

In order to explain why the domino process does not occur, an intermolecular version of the reaction was carried out [165]. Thus, a mixture of the tryptophan methyl ester and oct-1-ene were mixed together and submitted to hydroformylation under different reaction conditions. After 30 min of MW dielectric heating in THF [$(PPh_3)_3Rh(CO)H$ (0.01 equiv.)/XANTPHOS (0.04 equiv.), H_2/CO 827 kPa, THF, MW, 110°C], the corresponding imine was isolated in 56% yield (Fig. 33).

Attempts to cyclize the imine under MW irradiation in the presence of different acid additives were unsuccessful. This goal was obtained by refluxing the imine in toluene for 12 h in the presence of PTSA (the corresponding tricyclic product was obtained in 50% yield). This result suggests that the domino process depends on the success of the second reaction. Although there are several reports describing how MW accelerates the Pictet–Spengler reaction, conditions compatible with the MW-assisted hydroformylation process were not found.

Another interesting case is the failed attempt of synthesis of 13-methylprotoberberine (Fig. 34) [166, and references cited therein].

The process starts with a suitable substituted styryl substrate which was submitted under hydroformylation conditions in autoclave [$Rh(CO)_2$acac, BIPHEPHOS, THF, 80°C, H_2/CO 700 kPa, 1:1), 12 h, $BF_3{\cdot}OEt_2$ were the experimental conditions adopted]: the homoberberine was obtained in 45% yield. Other attempts gave the simultaneous formation of two compounds, an amide and an azapinone (Fig. 35), the

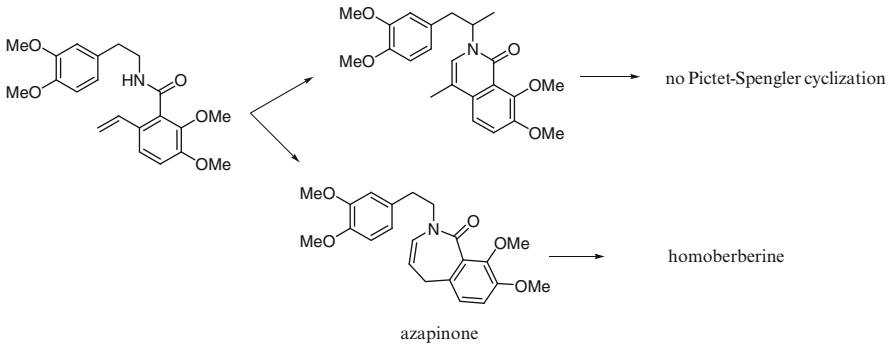


Fig. 35 Evidence for the failed synthesis of 13-methylprotoberberine: the amide intermediate is favored with respect to the corresponding acyliminium ion thanks to the strong conjugation with the aromatic ring

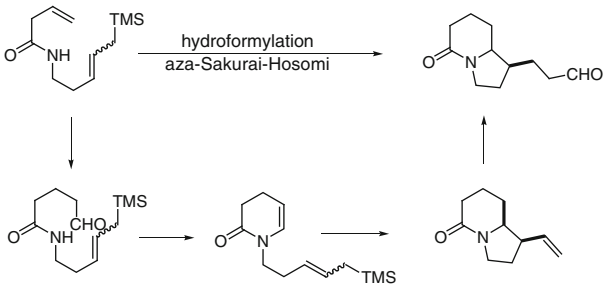


Fig. 36 Domino hydroformylation by aza-Sakurai-Hosomi cyclization

latter originating from abnormal linear hydroformylation of the styryl type double bond. Interestingly, the amide, coming from the branched aldehyde was by far the major adduct.

The amide did not cyclize if submitted separately to Pictet–Spengler cyclization (Fig. 35), whereas the azapinone gave the homoberberine in good yield. Probably the formation of the acyliminium ion is disfavoured with respect to the amide because of a strong conjugation with the aromatic ring. Thus, the fate of the Pictet–Spengler reaction influences the overall domino process proceeding exclusively towards homoberberine instead of the expected 13-methylprotoberberine.

5.3 On Allylsilanes

The allylsilane is another nucleophile that can react with an (acyl)iminium ion. The case of the domino hydroformylation aza–Sakurai cyclization with the formation of indolizidine [165] is reported in Fig. 36 in the presence of [Rh(acac)$(CO)_2$]/BIPHEPHOS as before.

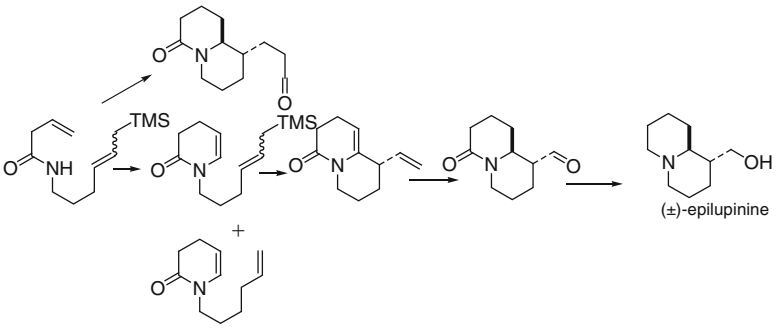


Fig. 37 Synthesis of the quinolizidine alkaloid (±)-epilupinine

Under hydroformylation conditions the starting silane generates the corresponding linear aldehyde, the process exclusively involving the more favored terminal double bond. The latter cyclizes to a bicyclic alkene which can undergo further hydroformylation towards a final linear aldehyde. In this sequence, two cycles and nine new bonds are formed in the same chemical operation. The reaction sequence can be stopped at each singular step, depending on the solvent and the acid additives, and the single intermediates can be isolated and/or employed in successive reactions. The linear aldehyde is obtained in 78% yield in THF with PPTS (5 mol%). In this structure, the presence of the internal double bond allows a subsequent aza–Sakurai–Hosomi reaction to an enamide. The latter isolated and treated with 4 equiv. of trifluoroacetic acid (TFA) in CH_2Cl_2 gives a bicycle with an exocyclic double bond as a mixture of two diastereomers (*cis*/*trans* 90:10) in 89% yield. It was also possible to isolate this alkene with the same diastereoselectivity in a one-pot operation (82% yield) if the hydroformylation was carried out without acid additive, and after the autoclave had been cooled and degassed, TFA was added at room temperature. If the bicyclic alkene was submitted under *oxo* conditions without acid additive the corresponding bicyclic aldehyde was obtained (78% yield). The same product can also be prepared (63% yield) in a domino reaction by mixing allylsilane in CH_2Cl_2 with 1 equiv. of TFA under hydroformylation conditions (12 h at 55°C). The best result [69% yield, diastereoselectivity (*cis*/*trans* 90:10)] was obtained by using 0.5 equiv. of $BF_3{\cdot}Et_2O$ in THF.

The allylsilane in Fig. 37 has been used as starting material for the synthesis of the quinolizidine alkaloid (±)-epilupinine [165]. When the silane was submitted to cyclizative hydroformylation in an autoclave in the presence of an acid additive, the quinolizinyl aldehyde was formed with good diastereoselectivity, the *oxo* of the exocyclic double bond also occurring. If the same reaction was performed sequentially omitting the Lewis acid during the hydroformylation step, the final linear hydroformylation did not proceed; instead a quinolizidine with exocyclic double bond was isolated in good yield. This sequence has been applied to the synthesis of (±)-epilupinine via ozonolysis of the double bond to give an aldehyde which was reduced to the final product (Fig. 37).

Under MW dielectric heating under different conditions, the overall domino process did not go to completion and a cyclic enamine was the main product isolated together with a small amount (20%) of the product of protodesilylation. Attempts to optimize the reaction were not successful. However, the enamine cyclizes in the presence of TFA to give the quinolizidine with an exocyclic double bond.

This example seems to indicate that microwave conditions are limited by the sensitivity to the nucleophile and then MW irradiation and autoclave heating are complementary for performing hydroformylations.

6 Conclusions

The examples depicted demonstrate that the chemo-, regio-, and stereoselectivity of the hydroformylation reaction can be modified by changing the reaction conditions and by using suitable ligands. Indeed, the importance of the organic part structure in this organometallic reaction is still more evident. The *oxo* process introduces the useful aldehyde function but in terms of synthetic efficiency the reaction suffers from the fact that it provides only a one carbon chain elongation. If the olefin substrate is properly designed, it becomes the starting point for a sequence of reaction steps to more complex molecular architectures. In summary a very important parameter, which determines the ratio of aldehydic products of hydroformylation and then the synthetic potentialities of the reaction, is the structure of the olefinic substrate itself. Imagination could be very important in the future for the chemist who will take care of hydroformylation, a reaction which, although old, is still intriguing.

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Hydroformylation in Natural Product Synthesis

Roderick W. Bates and Sivarajan Kasinathan

Abstract The application of hydroformylation to the synthesis of natural products and natural product-like molecules is surveyed.

Keywords Alkaloid · Hydroformylation · Tetrahydropyran

Contents

Abbreviations

Ac	Acetyl
acac	Acetylacetonate
aq	Aqueous

R.W. Bates (✉) and S. Kasinathan
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore, Singapore 637371
e-mail: Roderick@ntu.edu.sg

B:L	Branched:linear ratio
BDP	Bisdiazaphospholane
BINAPHOS	2-Diphenylphosphino-1,1′-binaphthalene-2,2′-diylphosphite
BIPHEPHOS	6,6′-[(3,3′-Di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl- 2,2′-diyl) bis(oxy)]bis(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin)
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
Cbz	Benzyloxycarbonyl
CDG	Catalyst directing group
cod	Cyclooctadiene
conv	Conversion
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DIBALH	Diisobutylaluminum hydride
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium
dr	Diastereomer ratio
DuPHOS	1,2-Bis[2,5-di-*iso*-propylphospholano]benzene
ee	Enantiomer excess
gem	Geminal
h	Hour(s)
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
IBX	2-Iodoxybenzoic acid
Ipc	Isopinocampheyl
i-Pr	Isopropyl
LiHMDS	Lithium bis(trimethylsilyl)amide
m-CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
mol	Mole(s)
n-hept	*n*-Heptyl
NMO	*N*-Methylmorpholine-*N*-oxide
Nu	Nucleophile
o-DPPB	*Ortho*-diphenylphosphanylbenzoyl
PDC	Pyridinium dichromate
PFL	*Pseudomonas florescens* lipase
Ph	Phenyl
PMP	*p*-Methoxyphenyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
pTSA	*p*-Toluenesulfonic acid

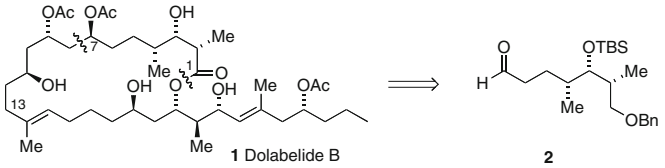
Pv	Pivaloyl
py	Pyridine
rt	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
Temp	Temperature
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl (triflyl)
TFA	Trifluoroacetic acid
THP	Tetrahydropyran-2-yl or tetrahydropyran
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-ethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Tr	Triphenylmethyl (trityl)
Ts	Tosyl 4-toluenesulfonyl
XANTPHOS	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

1 Introduction

As with alkene metathesis, hydroformylation was serendipitously discovered in industry. The original conditions employed for bulk chemical manufacture would be considered to be "brutal" by organic chemists. This may be the reason why, historically, uses of hydroformylation for the synthesis of natural products and complex natural product like molecules are scarce in the literature. With the development of much milder conditions and greater appreciation of stereochemical control issues, this situation is starting to change. Hydroformylation allows the formation of a carbon–carbon bond, often highly chemoselectively, under neutral conditions. Application of this reaction to the synthesis of complex molecules is increasing.

2 Synthesis of Aldehydes as Intermediates for Natural Product Synthesis

Aldehydes have always played a prominent role in organic synthesis, as targets in themselves, and mostly as intermediates. This is particularly for subsequent carbon–carbon or carbon–nitrogen bond formation. While there are various methods available for the introduction of aldehydes, the most common is, undoubtedly, the oxidation of alcohols. Hydroformylation offers an alternative. Not only is the reaction atom efficient, but it occurs under neutral conditions and tolerates a wide



Scheme 1 Dolabelide retrosynthesis

range of functional groups. Hydroformylation, thus, offers a route to aldehydes that can be significantly more efficient than the alternatives. The starting materials for hydroformylation, alkenes, may also be introduced by a number of methods, with asymmetric allylation becoming of greater and greater importance. The alkene functional group may also be carried through many standard synthetic steps without any need for protection.

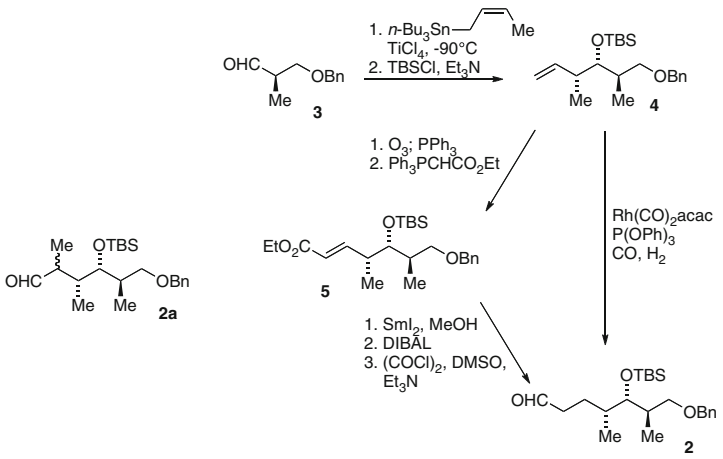
Dolabelide B **1**, isolated from the sea hare *Dolabella auricularia*, has been shown to exhibit cytotoxicity [1]. Keck and McLaws required aldehyde **2** as an intermediate in a synthesis of the C_1–C_{13} segment (Scheme 1) [2].

Aldehyde **2** was initially synthesized via crotylstannylation chemistry through a sequence of seven steps (Scheme 2). Alkene **4** was prepared from the aldehyde **3** using asymmetric crotylation to introduce the additional stereocenters and establish the *syn–anti* stereochemistry. Alkene **4** could then be converted to aldehyde **2** in 46% yield by a five step sequence involving ozonolysis of the alkene, Wittig olefination, selective alkene reduction, which required the use of samarium(II) iodide, and then a reduction–oxidation pair. It was recognized that out of these seven steps, a five step sequence was equivalent to hydroformylation of alkene **4**. Indeed, hydroformylation of alkene **4** gave aldehydes **2** and **2a** with a linear to branched ratio of 96:4, respectively, and an isolated yield of 82% (Scheme 2), easily replacing the original more cumbersome and lengthy approach.

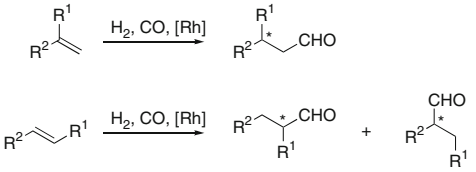
2.1 Applications of Diastereoselective Hydroformylation

While hydroformylation of a monosubstituted alkene simply yields an aldehyde, hydroformylation of a *gem*-disubstituted alkene also generates a new stereogenic center. Further, hydroformylation of a 1,2-disubstituted alkene can yield either or both of two regioisomers, as well as a new stereogenic center (Scheme 3). For hydroformylation of these kinds to be useful, the new stereocenter must be controlled. One way to achieve this goal is to employ a directing group within the substrate. As most functional groups in organic synthesis are poor ligands for rhodium, a temporarily attached group, sometimes called a catalyst directing group or CDG, can be used.

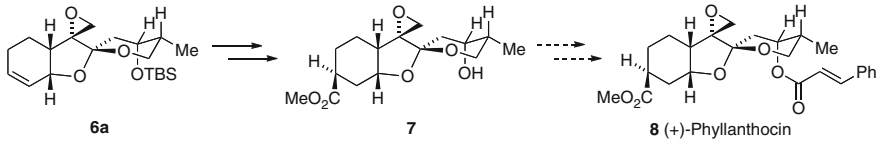
Burke et al. [3–5] worked on the total synthesis of (+)-phyllanthocin **8** which is a methanolysis product of the bisabolane glycoside phyllanthoside obtained from the



Scheme 2 Synthesis of the dolabelide C_1–C_7 fragment

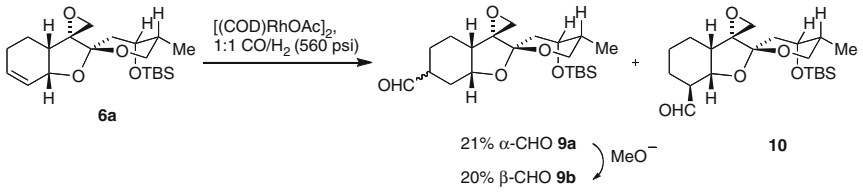


Scheme 3 Alkene hydroformylation: stereo- and regiochemical issues

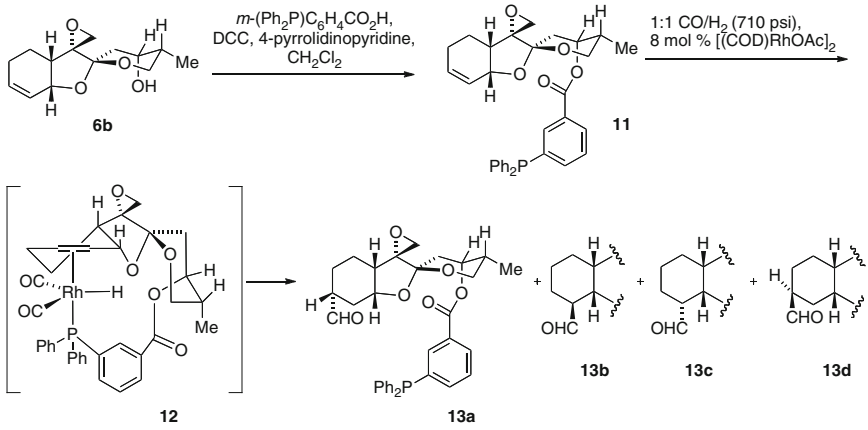


Scheme 4 Phyllanthocin synthesis

root extract of the Central American plant *P. accuminatus* Vahl [6, 7]. They had multiple concerns in mind when synthesizing this molecule and one of the major concerns was to avoid complications in accommodating the C3 carbomethoxy group until a late stage of the synthesis (Scheme 4). These concerns proved to be valid as, despite subjecting substrate **6a** to hydrozirconation [8, 9] or hydroboration or oxymercuration/demercuration based methodologies, only limited success was achieved. It was suggested that the lack of reactivity could be due to other Lewis basic sites in **6a**, or to unfavorable steric and electronic factors reducing the reactivity of the allylic ether. It was found possible to introduce the carbomethoxy group via a multistep sequence involving the Corey–Tius procedure [10] to afford descinnamoylphyllanthocin **7** and its C3 epimer. Although this formally completed a synthetic route to (+)-phyllanthocin **8**, this method for C3 functionalization was deemed to be unreliable and tedious.



Scheme 5 Hydroformylation in phyllanthocin synthesis

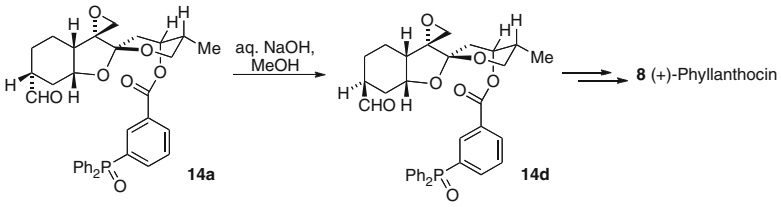


Scheme 6 Directed hydroformylation in phyllanthocin synthesis

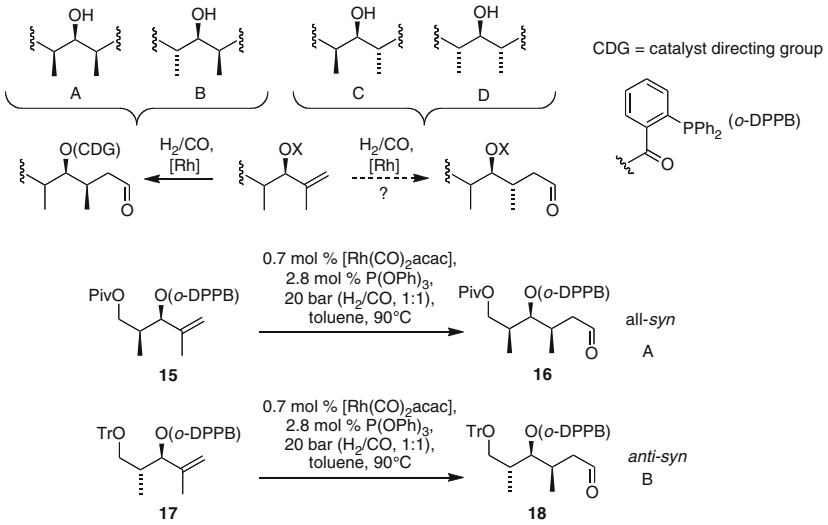
Hence, Burke et al. turned to hydroformylation (Scheme 5). Their initial attempt only produced partially satisfying results, whereby the C3-α- and C3-β-formyl products **9a** and **9b** were isolated in 21% and 20% yield, respectively, together with the C4-formyl product **10** that was isolated in 12% yield. Luckily, both the C3 epimers could be used for the synthesis of (+)-phyllanthocin due to the fact that the undesired epimer **9a** could be equilibrated with NaOMe/MeOH at 25°C to give a 2.3:1 mixture favoring the desired epimer **9b** in 80% yield.

In efforts to improve the hydroformylation reaction, Burke et al. ventured into intramolecular phosphine-directed hydroformylation (Scheme 6). Burke subjected substrate **11** (made from coupling *m*-(diphenylphosphino)benzoic acid to the alcohol **6b**) to hydroformylation conditions which led to a mixture of aldehydes **13a–d** in a ratio of 7.7:1:1:0.3 via the intermediate **12**. The combined yield of the desired C3-formyl isomers **13a** and **13d** was achieved in 72% isolated yield.

Taking advantage of the equilibration reaction with aqueous NaOH/MeOH, the phosphine oxide (phosphine oxide was used to avoid complications from handling the air-sensitive phosphine) of the major C3-formyl isomer **14a** was converted to the desired epimeric aldehyde **14d** in 73% yield, with an 18% recovery of **14a** (Scheme 7). The aldehyde **14d** was then submitted to a series of steps to obtain (+)-phyllanthocin **8** in 82% yield.



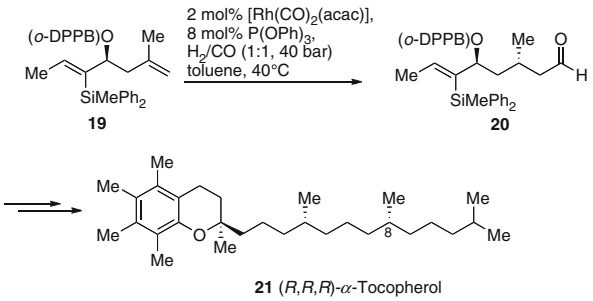
Scheme 7 Completion of phyllanthocin synthesis



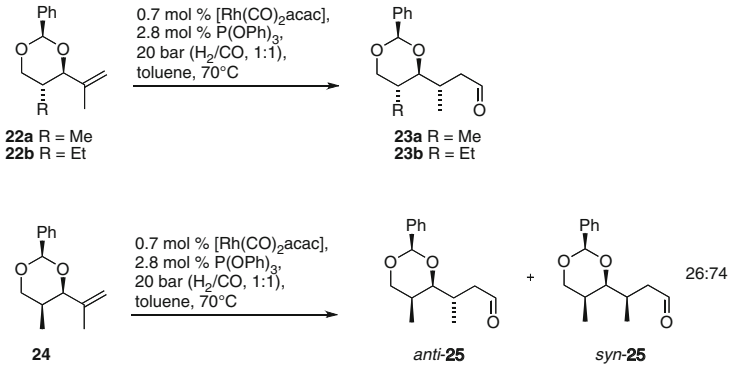
Scheme 8 Access to stereotriads by directed hydroformylation. Adapted with permission from [11]. Copyright (2001) American Chemical Society

Breit and Zahn developed methodology utilizing hydroformylation to generate stereotriads [11], which are short subunits of polypropionate chains consisting of an alternating methyl-hydroxyl-methyl array [12]. From the four different stereotriads differentiated by Breit and Zahn (**A**–**D**, Scheme 8), stereotriads **A** and **B** were synthesized in excellent yield and diastereoselectivities [13] using diastereoselective hydroformylation of methallyl alcohol derivatives **15** and **17** which each carry a catalyst directing group (CDG) [14–16].

This strategy was employed in a synthesis of (*R*, *R*, *R*)-α-tocopherol **21** (Scheme 9) [17], which is the most prominent and biologically most active naturally occurring member of the compounds covered by the term vitamin E [18, 19]. Aldehyde **20** was obtained when alkene **19** was subjected to *o*-DPPB-directed rhodium-catalyzed hydroformylation. The reaction proceeded with good diastereoselectivity (dr = 91:9) in 81% yield. The stereogenic center generated by this reaction then became the C8 stereogenic center of α-tocopherol **21**, while the phosphinobenzoate ester was lost in an S_N' cuprate displacement.



Scheme 9 α-Tocopherol synthesis

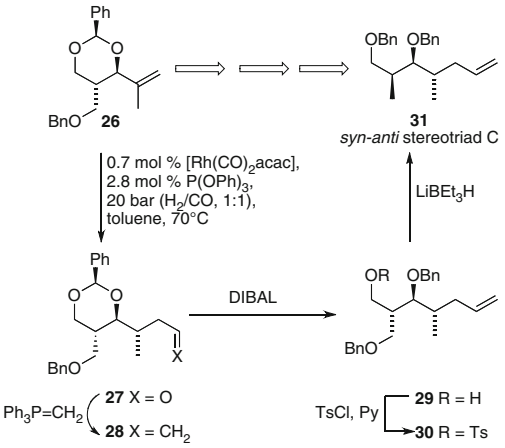


Scheme 10 Access to stereotriads by conformational control

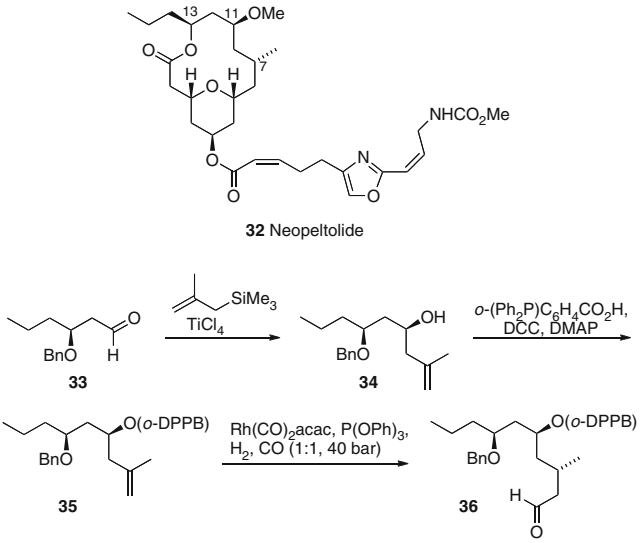
However, using the CDG-controlled hydroformylation of methallyl alcohol derivatives with *o*-diphenylphosphanyl benzoate (*o*-DPPB), only *syn*- products can be obtained. Alternatively, the inherent conformation of the substrate can be used to influence the formation of the new stereogenic center. Thus, Breit and Zahn devised a new model taking advantage of *syn*-pentane interactions to achieve *anti*-selective hydroformylation. The model was tested by subjecting benzylidene acetals **22a**, **22b**, and **24** to hydroformylation conditions (Scheme 10). The aldehydes **23a** and **23b** (stereotriad **D**) were obtained in good yield and excellent diastereoselectivity (*anti*: *syn* $\geq$ 99:1) but the reaction of the *syn*-acetal **24** proceeded slowly to give, in low yield, a mixture of *anti*-**25** and *syn*-**25** with reversed diastereoselectivity.

Therefore, to achieve the *anti*-selective hydroformylation for the construction of stereotriad **C**, a longer sequence had to be adopted (Scheme 11). This alternative involves hydroformylation of benzyloxy-substituted acetal **26** and converting the reactive aldehyde **27** via Wittig olefination to alkene **28**. Regioselective benzylidene ring opening with DIBAL and reductive removal of the alcohol function gave the desired *syn–anti* stereotriad building block **31** in diastereomerically pure form.

Directed hydroformylation was employed in a synthesis of neopeltolide **32**. This 12-membered macrolide marine natural product is a potent inhibitor of tumor proliferation and has attracted extensive interest from synthetic organic chemists

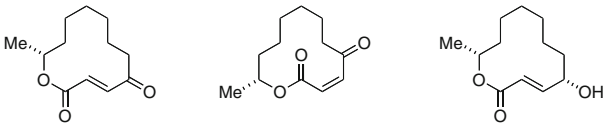


Scheme 11 Access to stereotriads C



Scheme 12 Directed hydroformylation in neopeltolide synthesis

([20]; for a review see [21]). Directed hydroformylation was employed in one synthesis to establish the C7 stereogenic center (Scheme 12) [22]. The diol derivative **34** was prepared by diastereoselective methallylation of aldehyde **33**. After installation of the catalyst directing group, hydroformylation gave the desired aldehyde **36** with 5:1 diastereoselectivity.



37 (+)-Patulolide A **38** (+)-Patulolide B **39** (+)-Patulolide C

Scheme 13 The patulolides

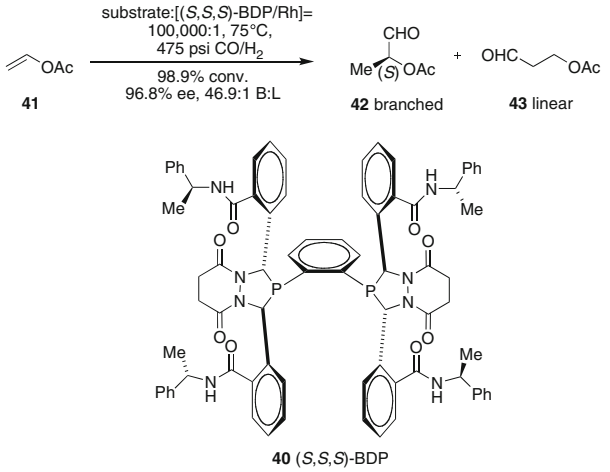
2.2 Asymmetric Hydroformylation Using Ligand Controls

The new stereogenic center may also be controlled by the use of chiral ligands. Numerous ligands have been proposed for asymmetric hydroformylation, and this chemistry offers good prospects for the asymmetric synthesis of natural products. Burke reported a very short, novel, and high yielding synthesis of (+)-patulolide C **39** via asymmetric hydroformylation [23]. (+)-Patulolides A, B, and C **37–39** were discovered by Yamada in 1985 from the culture filtrate of *Penicillium urticae* S11R59 mutant. They exhibit both antifungal and antibacterial activities (Scheme 13) [24, 25].

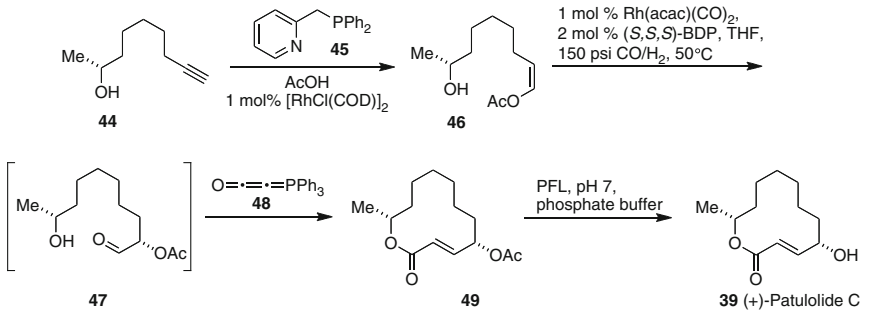
The Landis group developed the (*S*, *S*, *S*)-bisdiazaphospholane [(*S*, *S*, *S*)-BDP] ligand **40**, and its enantiomer, which display high activity with very high enantio- and regioselectivity for a variety of olefins [26–30]. Vinyl acetate **41** is one such example where it reacts exceptionally well, favoring the branched aldehyde **42**, with high enantioselectivity, over the linear aldehyde **43** (Scheme 14), giving access to lactaldehyde derivatives (see [28]).

Rhodium catalyzed hydroacetoxylation of alkyne **44** in the presence of pyridyl phosphine ligand **45** afforded enol acetate **46** in 82% yield and >95% regio- and stereoselectivity [31]. Enol acetate **46** was then subjected to asymmetric hydroformylation conditions using Rh(acac)$(CO)_2$ catalyst with the (*S*, *S*, *S*)-BDP ligand **40** to afford the α-acetoxyaldehyde **47** with complete regiocontrol and high diastereoselectivity as only one aldehyde was observed by ^{1}H NMR. Aldehyde **47** was substantially pure and, thus, treated directly with Bestmann ylide **48** [32] led to the formation of 12-membered lactone **49** in 62% yield with complete *E*-selectivity. Acetate **49** was then deacetylated under neutral conditions using *Pseudomonas florescens* lipase [33] (PFL) to afford (+)-patulolide C **39** in 49% overall yield (Scheme 15).

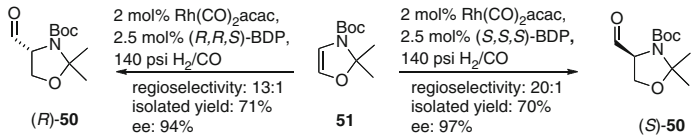
The (BDP) ligands have also been used for the synthesis of both enantiomers of Garner's aldehyde **50** [34] by asymmetric hydroformylation of the achiral alkene **50** [35]. Garner's aldehyde has typically been available as only one enantiomer, starting from serine. Using hydroformylation, both enantiomers could be prepared in moderate yield but with excellent regio- and enantioselectivity (Scheme 16).



Scheme 14 Asymmetric hydroformylation of vinyl acetate



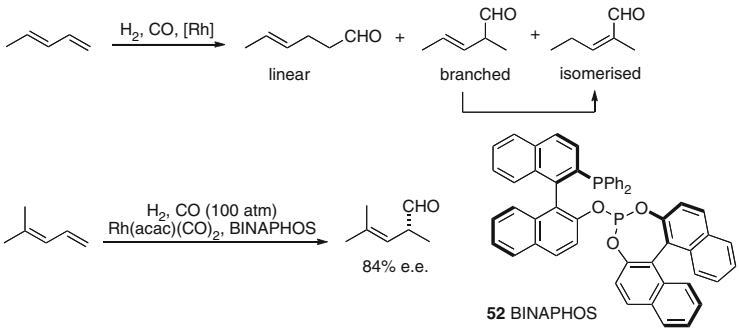
Scheme 15 Patulolide C synthesis



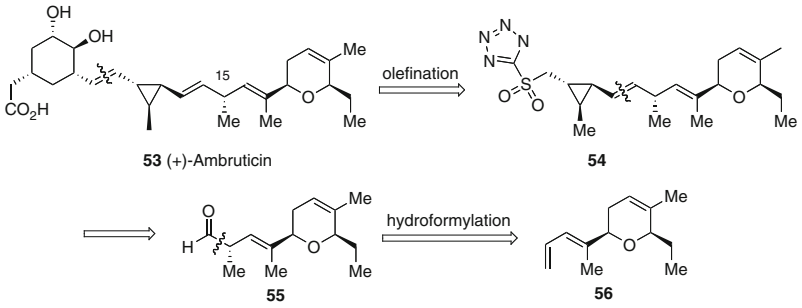
Scheme 16 Synthesis of Garner's aldehydes

2.3 Hydroformylation of Dienes

Hydroformylation of dienes has long been problematic, often giving mixtures of isomers (Scheme 17). If mono-hydroformylation is considered (and alkene stereochemistry is disregarded), then three products may be predicted: the linear and branched products plus the alkene isomerization product of the latter. Nozaki et al. were able to address this longstanding problem, favoring the branched isomer with suppression of isomerization, and controlling stereochemistry by the use of



Scheme 17 Diene hydroformylation



Scheme 18 Ambruticin retrosynthesis

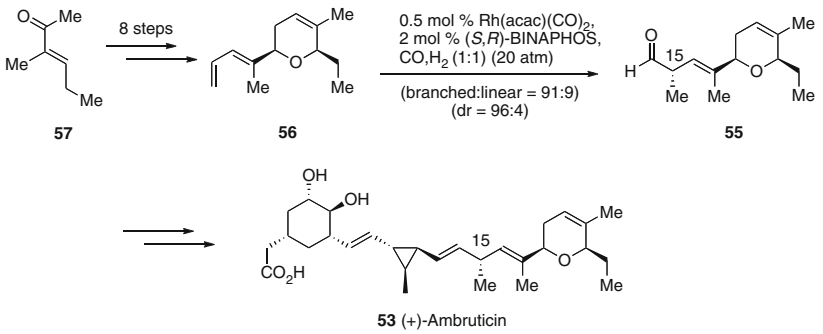
BINAPHOS **52** as the ligand [36]. The favoring of the branched isomer was attributed to the participation of η^3-allyl complexes of rhodium.

Jacobsen [37] reported the total synthesis of a novel antifungal agent called ambruticin **53** that was isolated from fermentation extracts of the myxobacterium *Polyangium cellulosum* by Warner–Lambert scientists in 1977 [38]. They planned the synthesis via Kocienski–Julia olefination [39, 40] of sulfone **54** (Scheme 18). This sulfone would arise from aldehyde **55**.

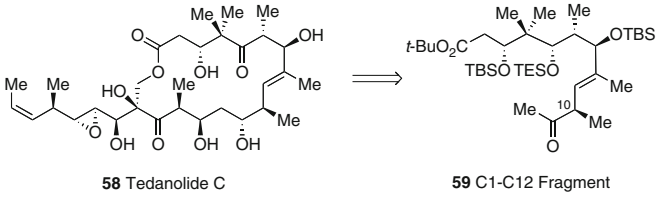
The key reaction in this synthesis involves the installation of the C15 stereocenter of fragment **55** by asymmetric hydroformylation reaction of a diene precursor **56**. The required diene **56** was prepared from α,β-unsaturated ketone **57**, and subjected to Nozaki's hydroformylation conditions. Aldehyde **55** was obtained with high regio- and diastereo-selectivity, which was then further reacted to give (+)-ambruticin **53** (Scheme 19).

Smith et al. [41] synthesized the C1–C12 fragment **59** of the marine natural product tedanolide C **58**, which was isolated from a species of *Ircina* sponge from the waters near Papua New Guinea [42] (Scheme 20).

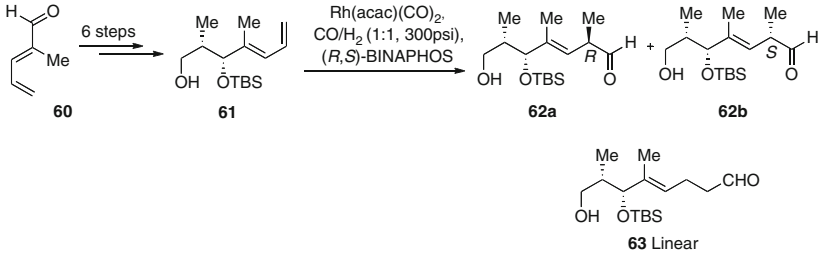
Due to stereochemical ambiguity at C10, synthetic flexibility was required, by establishing this stereocenter at a late stage with as many common intermediates as possible. Following the example set by Jacobsen in the synthesis of Ambruticin by



Scheme 19 Ambruticin synthesis



Scheme 20 Tedanolide retrosynthesis



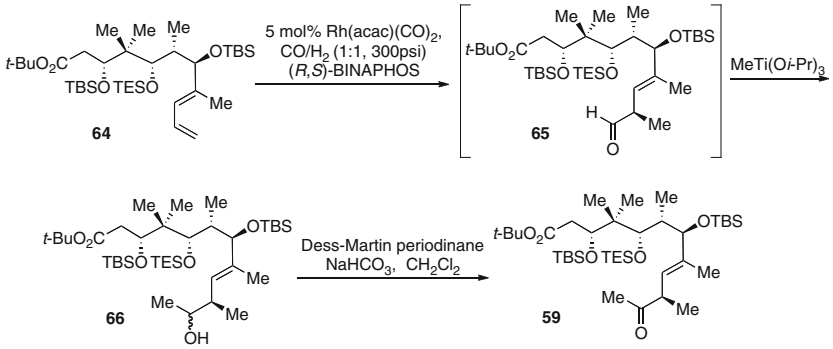
Scheme 21 Hydroformylation studies for tedanolide synthesis

way of an asymmetric diene hydroformylation, a model diene **61** was prepared (Scheme 21). The rhodium-catalyzed hydroformylation with a variety of ligands was investigated (Table 1). Nozaki's original conditions were found to be the best of those tested as (*R*, *S*)-BINAPHOS **52** (entry 6) led to a 93:7 ratio of C10 epimers **62a** and **62b**, accompanied by a small amount of the linear isomer **63**.

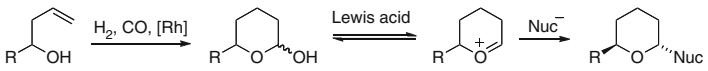
Application of these conditions to the actual intermediate **64** proceeded smoothly and with >95:5 diastereoselectivity. Although aldehyde **65** could be isolated, it was directly methylated and the resulting secondary alcohol **66** was oxidized to provide methyl ketone **59** as a single stereoisomer (Scheme 22). Use of (*S*,*R*)-BINAPHOS as the ligand gave the other diastereoisomer with the same efficiency.

Table 1 Hydroformylation in tedanolide synthesis

Entry	Ligand	Temperature (°C)	Time (h)	Branched:linear ratio	R/S
1	PPh_3	35	24	86:14	48:52
2	(*R*,*R*)-Chiraphite	35	72	100:0	57:43
3	(*R*,*R*)-Kelliphite	35	24	95:5	59:41
4	(*R*,*R*)-Ph-Bpe	35	24	–	–
5	(*R*,*R*)-Ph-Bpe	80	18	96:4	52:48
6	(*R*,*S*)-BINAPHOS	35	113	96:4	93:7
7	(*S*,*R*)-BINAPHOS	35	113	92:8	6:94



Scheme 22 Hydroformylation in tedanolide synthesis



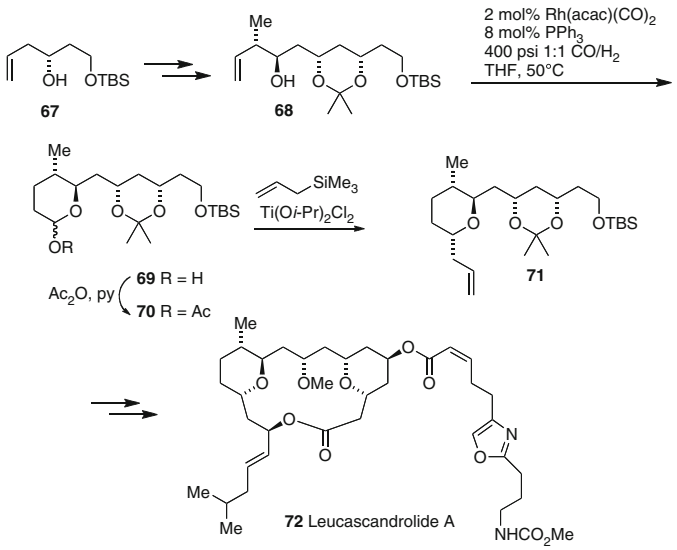
Scheme 23 Hydroformylation in THP synthesis

3 Tetrahydropyran Synthesis

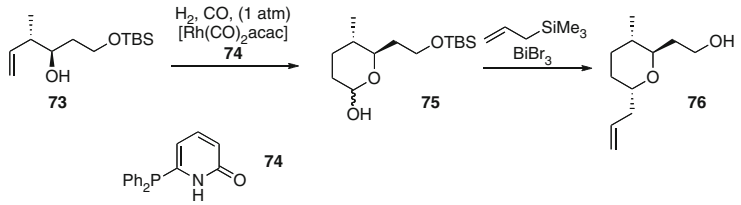
An aspect of aldehyde synthesis of particular usefulness is in the hydroformylation of homoallylic alcohols. This is because a hemiacetal will be formed directly. These are useful precursors of oxonium ions, allowing formation of a 2,6-disubstituted tetrahydropyran in a short sequence (Scheme 23). The final nucleophilic addition is typically under stereoelectronic control, leading to the *trans* product.

In the total synthesis of leucascandrolide A **72**, Leighton et al. introduced a THP ring into their molecule via a tandem hydroformylation/acetalization of the alkene **68** to give a ~1:1 anomeric mixture of hemiacetals **69** in 89% yield (Scheme 24) [43]. After conversion to the corresponding anomeric acetates **70**, allylation proceeded with better than 10:1 diastereoselectivity.

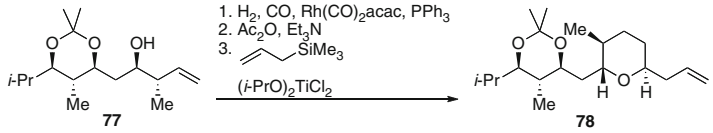
A related strategy for the formation of this tetrahydropyran ring was developed by Floreancig (Scheme 25) [44]. The homoallylic alcohol **73**, available by asymmetric crotylation, was subjected to hydroformylation under conditions developed by Breit using the phosphinopyridone ligand **74** [45, 46] to give hemiacetal **75**. This



Scheme 24 Hydroformylation in Leucascandrolide synthesis according to Leighton



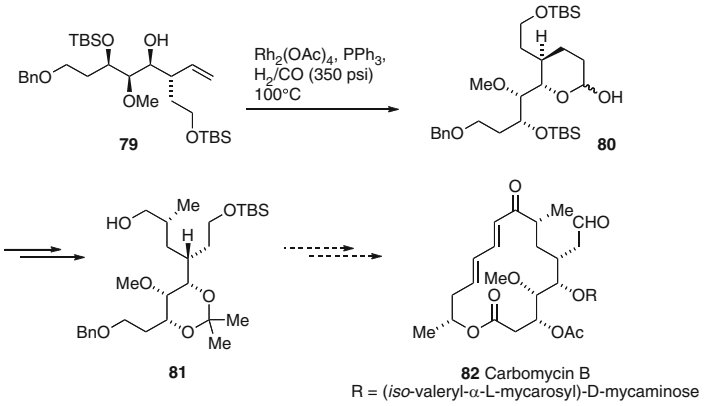
Scheme 25 Hydroformylation in Leucascandrolide synthesis according to Floreancig



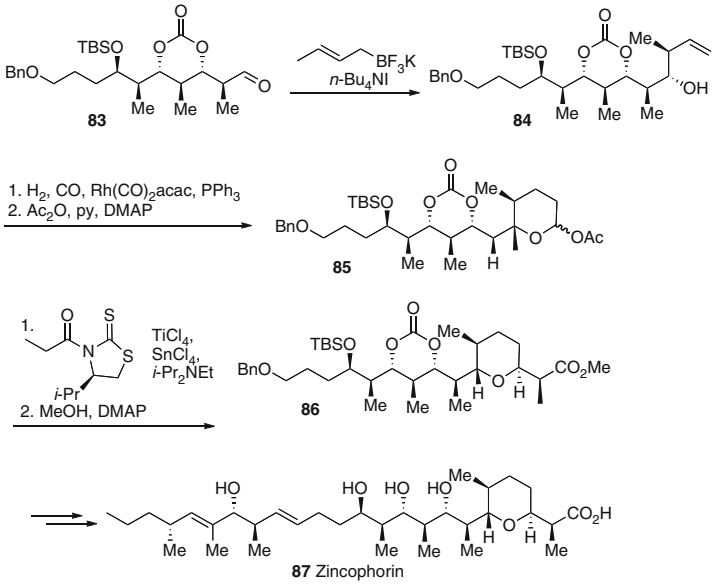
Scheme 26 Synthesis polyketide-like compounds

is notable as one of the few examples of hydroformylation being carried out at atmospheric pressure, with the two gases being delivered by balloons. The hydroxy group was then replaced by an axial allyl group under stereoelectronic control, with concomitant removal of the silyl ether, to give tetrahydropyran **76**. While the now free alcohol was extended using oxidation and Mukaiyama aldol chemistry, the allyl group was subsequently employed in cross metathesis.

A closely related series of transformations was employed to make polyketide-like compounds, such as tetrahydropyran **78** (Scheme 26) [47].



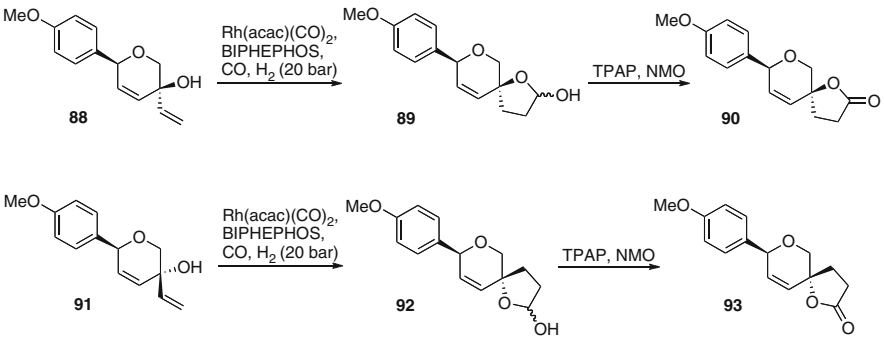
Scheme 27 Hydroformylation in carbomycin B synthesis



Scheme 28 Hydroformylation in zincophorin synthesis

Similarly, in a formal synthesis of carbomycin B **82**, Wuts et al. employed tetrahydropyran intermediates, although this ring is not present in the final molecule (Scheme 27). The THP was generated by a tandem regioselective hydroformylation/acetalization of the alkene **79** to give the alcohol **80**, which was then further converted to the formal synthesis product **81** through a series of steps [48].

Zincophorin **87** is an ionophore product with a particular affinity for both zinc and magnesium cations, isolated from *Streptomyces griseus* [49]. Leighton proposed to construct the tetrahydropyran ring by the combination of hydroformylation and alkylation (Scheme 28) [50]. The required homoallylic alcohol **84** was prepared by



Scheme 29 Hydroformylation in spirocyclic butyrolactone synthesis

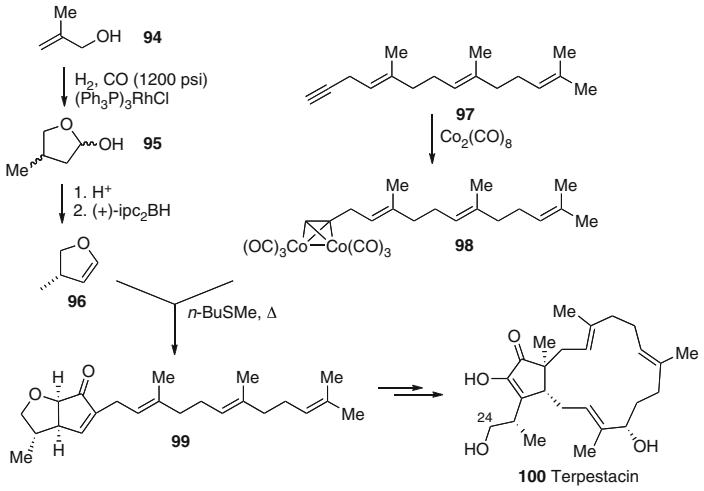
the addition of a Batey crotyl trifluoroborate [51] to aldehyde **83** under substrate control. Hydroformylation gave a lactol, which was converted into the corresponding acetate **85**. Successful use of acetate **85** in the subsequent alkylation process depended on both the expected axial attack by the nucleophile, which was obtained, and the facial selectivity of the nucleophile to control the stereochemistry α to the eventual carboxylic acid. Ultimately, this aspect was controlled by the use of a chiral auxiliary. The auxiliary was then removed by methanolysis, allowing the remainder of the molecule to be built up through the agency of the benzyl ether.

4 Tetrahydrofuran Synthesis

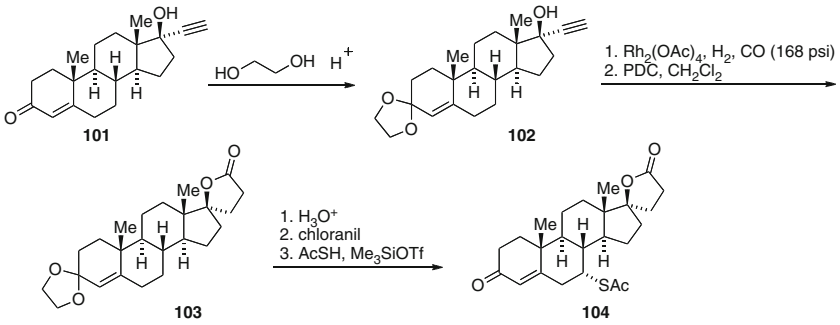
Just as tetrahydropyrans are available by hydroformylation of homoallylic alcohols, tetrahydrofurans, as well as related structures such as butyrolactones, must be available by the hydroformylation of allylic alcohols.

Spirocyclic γ-butyrolactones play a key role as synthetic intermediates [52–54] for many natural products [55–58]. Schmidt introduced a novel approach to spirocyclic γ-butyrolactones, by combining ruthenium catalyzed ring-closing metathesis with rhodium-catalyzed hydroformylation-acetal formation sequence (Scheme 29) [59]. The utility of their approach was demonstrated by the synthesis of various substituted di- or tetrahydropyrans linked to lactones in a spirocyclic fashion. They also showed the advantage of utilizing the BIPHEPHOS ligand system [60], as it allows the differentiation between exocyclic and endocyclic C–C double bonds under hydroformylation conditions.

Terpestacin **100**, a fungal sesquiterpene natural product, has been found to inhibit the formation of syncytia, multinucleated cells involved in HIV [61], and to inhibit angiogenesis [62]. Jamison reported an efficient synthesis of this compound (Scheme 30), starting with the hydroformylation of methallyl alcohol **94** in a reaction that could be carried out on a mole scale [63]. After dehydration of the



Scheme 30 Hydroformylation in terpestacin synthesis

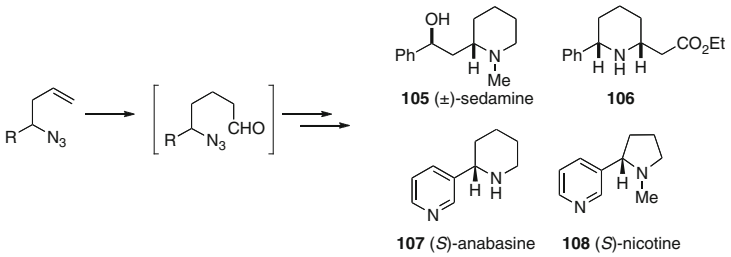


Scheme 31 Hydroformylation in spironolactone synthesis

resulting lactol **95**, the resulting dihydrofuran could be subjected to kinetic resolution under Brown's conditions to give the key building block **96** in >95% ee [64].

An interesting aspect of this synthesis is that the five-membered ring formed by hydroformylation is not actually present in the final product. The ring serves to ensure that the Pauson–Khand reaction with dicobalt complex **98**, which establishes the cyclopentenone, proceeds with high stereoselectivity due to the methyl substituent on dihydrofuran **96**. The ether ring present in bicycle **99**, created by hydroformylation, also serves to protect the C24 hydroxy group. Indeed, the protecting C–O bond is only cleaved in the final step of the synthesis.

Alkynes may also be used as the substrate in place of alkenes. Under the correct conditions they appear to undergo reduction prior to hydroformylation. This reaction was exploited to convert ethisterone **101** to spironolactone **104**, a diuretic and an aldosterone antagonist (Scheme 31). Protection of the ketone as a dioxolane was required for successful hydroformylation; otherwise the 4,5-alkene was affected.



Scheme 32 Piperidine and pyrrolidine alkaloids synthesized using hydroformylation

5 Alkaloid Synthesis Using Hydroformylation

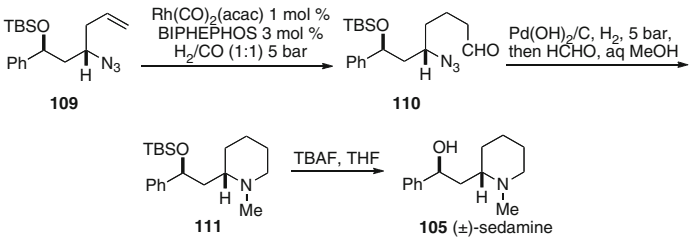
Breit et al. [65] have shown that homoallylic azides can undergo hydroformylation without affecting the azide function. In this way, a reactive nitrogen atom may be carried through a synthesis without the need for extensive protecting group strategies. Phosphites have been found to be the most appropriate ligands for this reaction as they do not undergo the Staudinger reaction with the azide under the reaction conditions. Phosphines, on the other hand, react readily with azides. Hence, Breit's ligand of choice was BIPHEPHOS, a sterically hindered bis-phosphite ligand that greatly favors the linear/branched ratio with a high turnover frequency (see [60]). With these practical concepts in place, a variety of alkaloids have become easily accessible (Scheme 32).

First, the well-known alkaloid (±)-sedamine **105** (see [65]; for the synthesis of *sedum* alkaloids in general, see [66]) was synthesized in three steps starting from the homoallylic azide **109**. Hydroformylation of the homoallylic azide **109** gave the aldehyde **110** which was reduced to the primary amine with Pearlman's catalyst in the presence of aqueous formaldehyde to give the cyclized methylated amine **111** that was deprotected to provide (±)-sedamine **105** (Scheme 33).

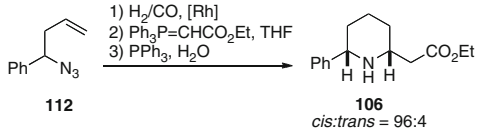
Second, 2,6-disubstituted piperidine **106** was obtained in a one-pot fashion, by hydroformylation/Wittig olefination/Staudinger/Michael addition reaction with an overall yield of 60% (Scheme 34).

Finally, the chiral pyridinyl-homoallylazide **113** was utilized in the synthesis of two major alkaloids from *Nicotiana tabacum*, (*S*)-anabasine **107** and (*S*)-nicotine **108** (Scheme 35). After hydroformylation of azido-alkene **113**, replacement of the syngas by hydrogen allowed reductive amination in the presence of Pearlman's catalyst to give (*S*)-anabasine in 81% yield and 94% ee. Alternatively, after hydroformylation of azido-alkene **113** and removal of syngas, addition of trifluoroacetic acid resulted in an intramolecular Schmidt rearrangement [67, 68] to give *N*-formyl pyrrolidine **114**. Tandem deformylation and Eschweiler–Clarke reaction provided (*S*)-nicotine **108** in 80% yield and 94% ee.

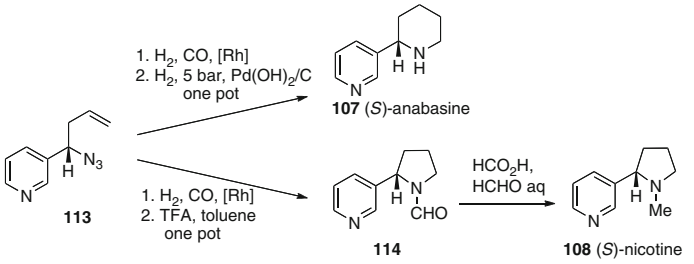
This strategy has been extended to encompass double hydroformylation with the syntheses of two naturally occurring quinolizidine alkaloids, (+)-lupinine **115** and (+)-epiquinamide **116** (Scheme 36) [69].



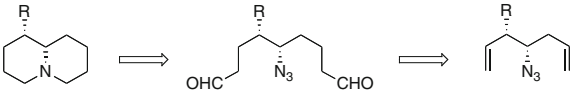
Scheme 33 Hydroformylation in sedamine synthesis



Scheme 34 One-pot hydroformylation-Wittig reaction-aza-Michael addition



Scheme 35 Hydroformylation in pyridyl alkaloid synthesis



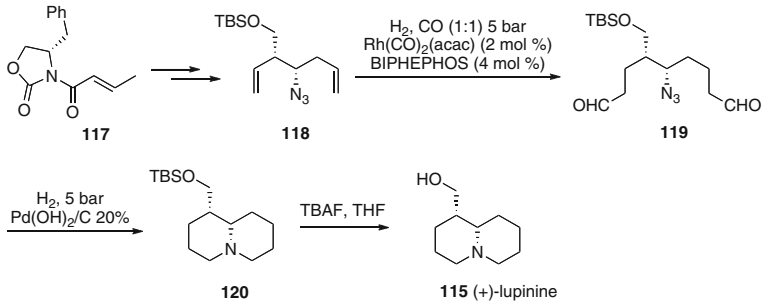
115 R = CH_2OH, (+)-lupinine
116 R = NHAc, (+)-epiquinamide

Scheme 36 Quinolizidine retrosynthesis

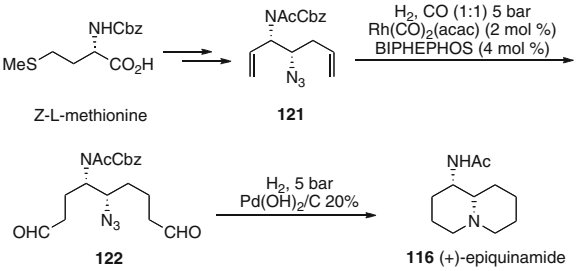
Hydroformylation of the intermediate homoallylic azide **118**, obtained in five steps from oxazolidinone **117**, gave the desired bis-aldehyde **119**. Tandem azide reduction-double reductive amination using Pearlman's catalyst gave the desired quinolizidine core **120** in 87% yield. De-protection with TBAF then gave (+)-lupinine **115** with an overall yield of 15% (Scheme 37).

Similarly, hydroformylation of the bishomoallylic azide **121**, obtained in nine steps from Cbz-L-methionine, and further reduction of azide **122** using Pearlman's catalyst gave (+)-epiquinamide **116** with an overall yield of 29% (Scheme 38).

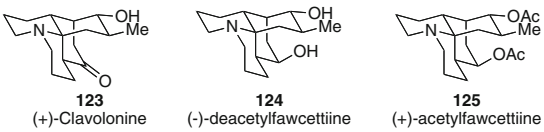
Catalyst directing groups have also been employed in the area of alkaloid synthesis. Breit has achieved stereoselective total syntheses of three lycopodium alkaloids:



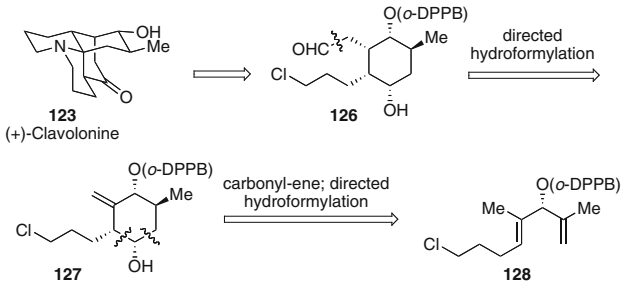
Scheme 37 Hydroformylation in lupinine synthesis



Scheme 38 Hydroformylation in epiquinamide synthesis



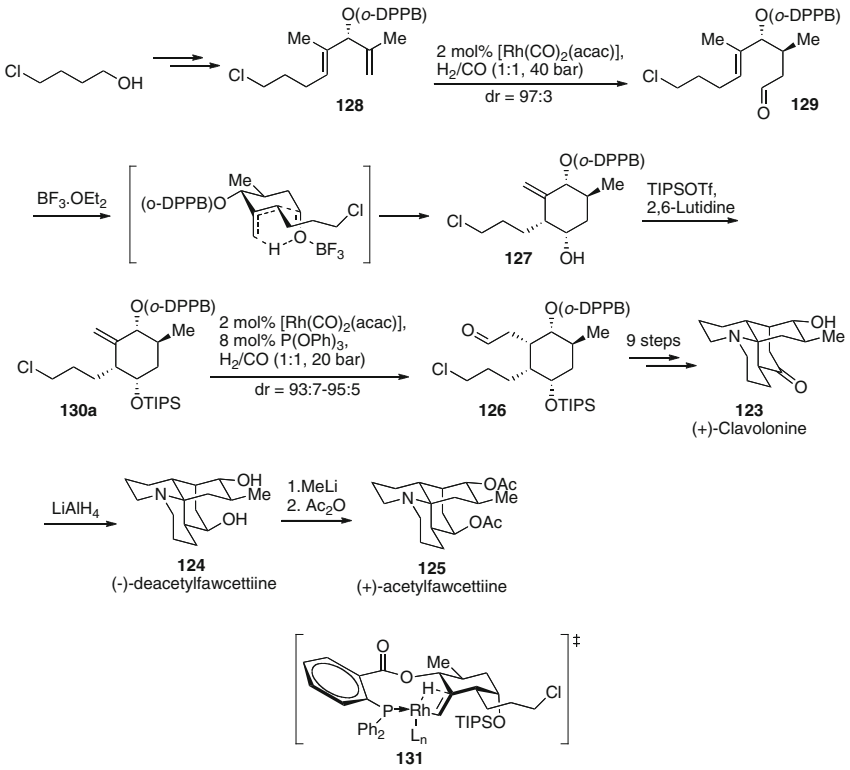
Scheme 39 Selected lycopodium alkaloids



Scheme 40 Clavolonine retrosynthesis

(+)-clavolonine **123**, (−)-deacetylfawcettiine **124**, and (+)-acetylfawcettiine **125** (Scheme 39) [70].

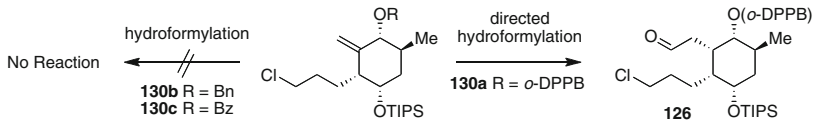
In the synthesis of (+)-clavolonine **123**, two hydroformylation reactions were employed, using the *o*-DPPB directing group (Scheme 40).



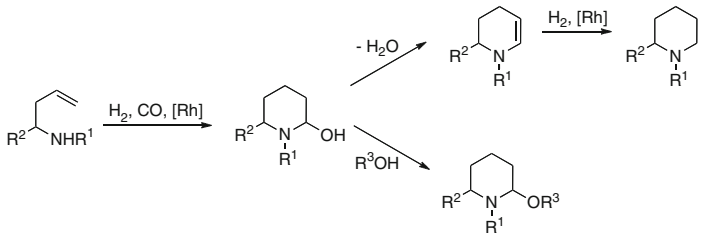
Scheme 41 Hydroformylation in clavolonine synthesis

o-DPPB ester **128** was synthesized in nine steps from 4-chlorobutanol. Hydroformylation of this ester was chemo-, regio-, and diastereoselective giving the *syn*-aldehyde **129** in excellent yield (dr = 97:3, 89%) with no reaction at the tri-substituted alkene (Scheme 41) [71, 72]. Following an intramolecular ene-reaction to form cyclohexanol **127**, the second directed hydroformylation step was attempted, but the diastereoselectivity was not as high as expected (dr = 71:29). The alcohol was, therefore, protected as a bulky TIPS ether [73] to create a greater conformational bias. Hydroformylation of TIPS ether **130a** then proceeded to give aldehyde **126** with much higher stereoselectivity (dr = 95:5) at C6. Aldehyde **126** could then be taken through to the three natural products. A transition state **131** has been proposed to explain the high diastereoselectivity.

To prove that the participation of the catalyst-directing group *o*-DPPB was essential in achieving both chemo- and diastereo-selectivity of this second hydroformylation step, control experiments were carried out by subjecting the analogous benzyl ether **130b** and the benzoate **130c** to the same hydroformylation conditions. No product formation was observed in either case. This is due to the low reactivity of simple 1,1-disubstituted alkenes in hydroformylation due to steric hindrance (Scheme 42).



Scheme 42 Control experiments in the clavolonine synthesis



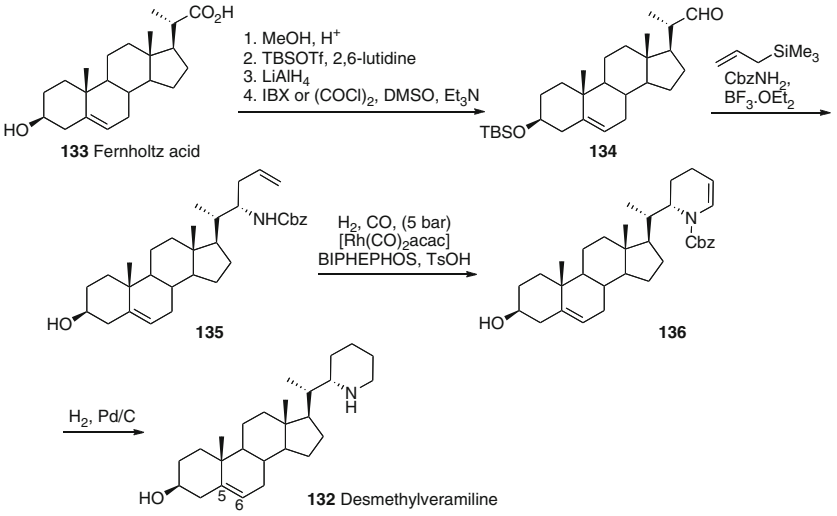
Scheme 43 Tandem hydroformylation-addition/condensation for alkaloid synthesis

6 Tandem Hydroformylation Processes for Alkaloid Synthesis

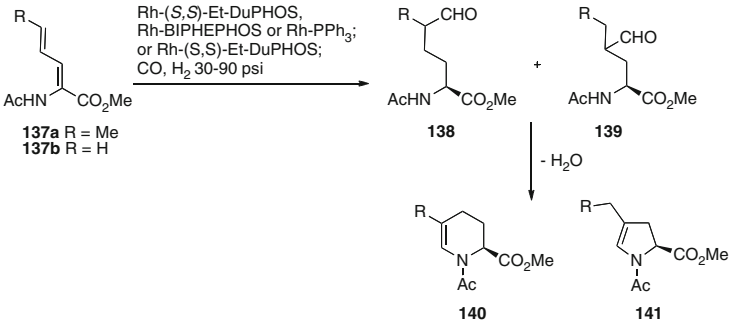
While azides are unaffected by the hydroformylation process, many other nitrogen functional groups will condense with the aldehyde that is formed (Scheme 43) [74]. While there are exceptions, in general, a primary amine will condense to give an enamine which will be further reduced in a tandem process. This process may be either inter- or intramolecular. On the other hand, amides and sulfonamides will add to the aldehyde. In some cases, elimination to the *N*-acyl or *N*-sulfonyl enamine is observed. Typically, the alkene is neither further reduced nor further hydroformylated. In alcohol solvents, an *N*,*O*-acetal is often formed. These processes are intramolecular, forming either five- or six-membered rings.

6.1 Nitrogen Nucleophiles

Desmethylveramiline **132**, a steroidal alkaloid, was desired in order to study its ability to inhibit the Sonic Hedgehog signaling pathway [75]. The Fernholtz acid **133** was selected as a suitable starting material (Scheme 44). The carboxylic group could be converted to an aldehyde **134** in a routine way. Subjection of aldehyde **134** to an aza-Sakurai–Hosomi process proceeded with excellent diastereoselectivity to give a homoallylic amine derivative **135**. Hydroformylation using BIPHEPHOS as the ligand in the presence of some acid to promote dehydration yielded the protected enamine **136**, which was reduced and deprotected in one pot to give the piperidine **132**. Neither transition metal catalyzed process affected the hindered 5,6-alkene.



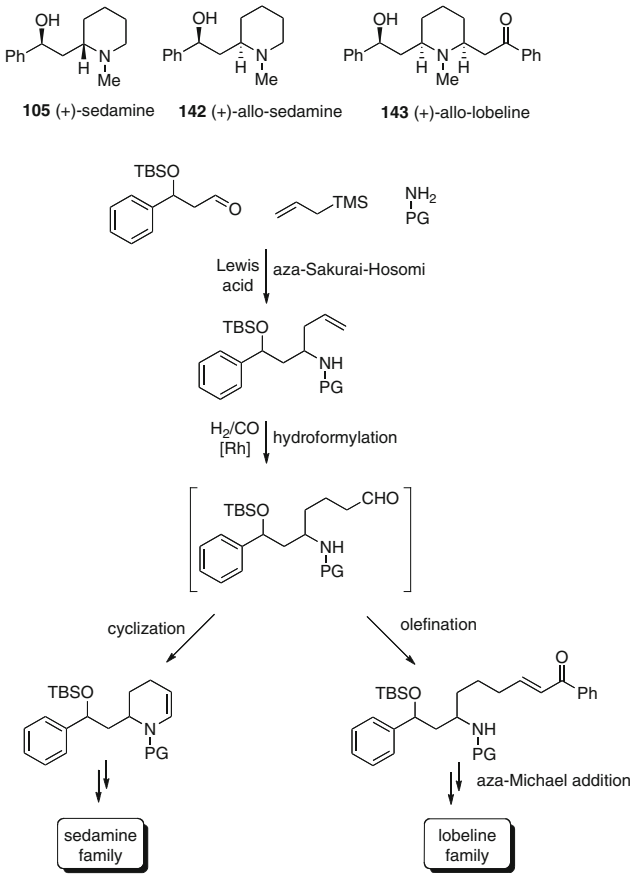
Scheme 44 Hydroformylation in desmethylveramiline synthesis



Scheme 45 Hydrogenation–hydroformylation reactions

Robinson et al. carried out hydrogenation of the dienamides **137a** and **137b** in the presence of both Rh-DuPHOS and either Rh-BIPHEPHOS or Rh-PPh_3 catalysts (Scheme 45). After completion of low pressure hydrogenation, the gas was vented and replaced by 1:1 CO/H_2 gas mixture and the temperature raised to 80°C. Good to very good yields of the heterocycles **140** and **141** with excellent enantioselectivity (>95% ee) was observed. It was also shown that Rh-DuPHOS itself can be used as an efficient catalyst for one-pot tandem hydrogenation–hydroformylation reactions although it needed slightly more harsh conditions than Rh-BIPHEPHOS and Rh-PPh_3 [76].

Mann et al. reported the use of the aza-Sakurai–Hosomi three-component reaction to generate *anti*-allylamines, which were used for the syntheses of piperidine alkaloids from the sedamine and lobeline families (Scheme 46) [77].

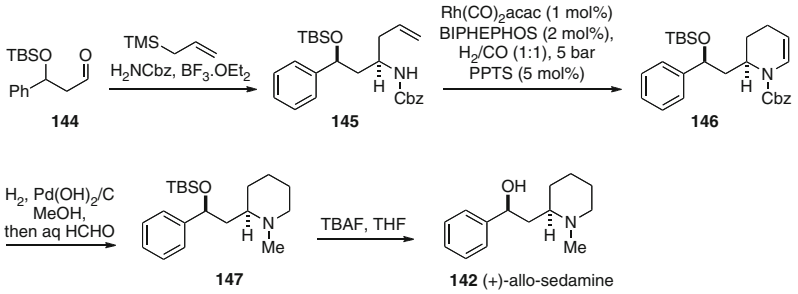


Scheme 46 A synthetic strategy for piperidine alkaloids

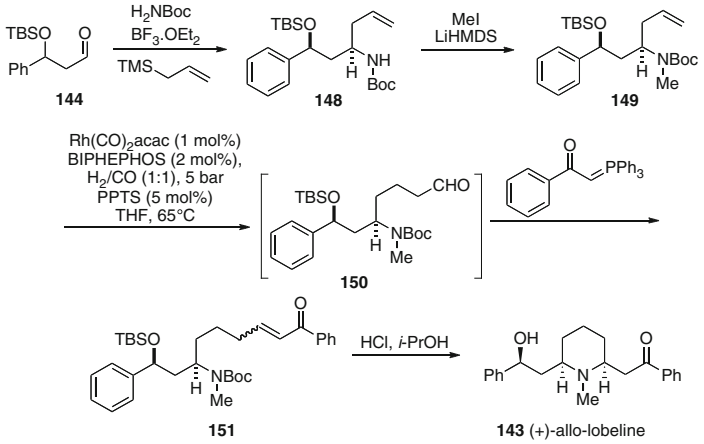
(±)-allo-Sedamine **142** was synthesized starting from aldehyde **144** that was converted to the homoallylamine **145** [78]. The homoallylamine **145** was then hydroformylated to give the *N*-acyl enamine **146**. Reduction in the presence of Pearlman's catalyst and formaldehyde resulted in tandem deprotection-methylation to furnish (±)-allo-sedamine **142** after cleavage of the TBS protecting group (Scheme 47) (see [79]).

Similarly, in the synthesis of (±)-allo-lobeline **143**, the protected homoallylamine **149** was subjected to a one-pot hydroformylation-Wittig olefination, a sequence initially described by Breit et al. [80], to give the enone **151** in 77% isolated yield, as a mixture of *E*- and *Z*-isomers (see [79]). Treatment of the enone **151** under acidic conditions allowed *N*-Boc deprotection followed by an aza-Michael reaction and desilylation to afford (±)-allo-lobeline **143** in 72% yield (Scheme 48).

The versatility of the aza-Sakurai–Hosomi hydroformylation strategy was further demonstrated by the syntheses of piperidines such as (±)-coniine **154** (64% overall yield for three steps), (±)-anabasine **107** (34% overall yield for



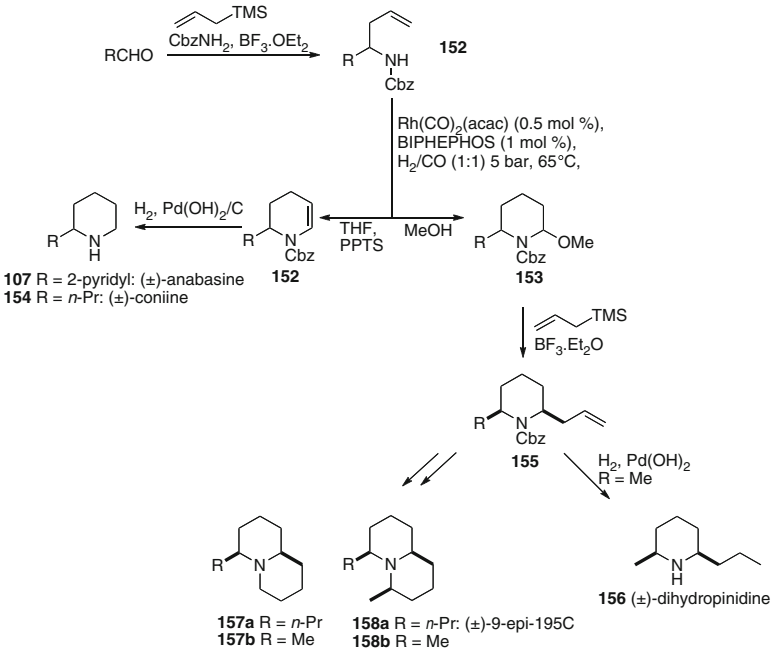
Scheme 47 Hydroformylation in allo-sedamine synthesis



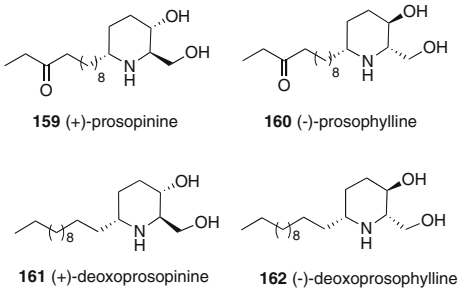
Scheme 48 Hydroformylation in allo-lobeline synthesis

three steps), (±)-dihydropinidine **156** (34% overall yield over four steps), (±)-9-*epi*-alkaloid 195C **158a** (27% overall yield over five steps), and other quinolizidines **157a**, **157b**, and **158b** (Scheme 49) [81].

Highly functionalized piperidine alkaloids are widespread in nature, such as (+)-prosopinine **159** and (−)-prosophylline **160** which were isolated from the leaves of *Prosopis africana* Taub and exhibit biological activity of medicinal interest (Scheme 50) ([82] and references cited therein). Similarly, their reduced analogues (+)-deoxoprosopinine **161** (selected syntheses of deoxoprosopinine [83–89]) and (−)-deoxoprosophylline **162** (selected syntheses of deoxoprosophylline [90, 91]) also exhibit similar biological properties. Ojima et al. utilized their previously developed methodology [92, 93] of rhodium-catalyzed hydroformylation of functionalized homoallylic amine intermediates in the synthesis of these alkaloids.



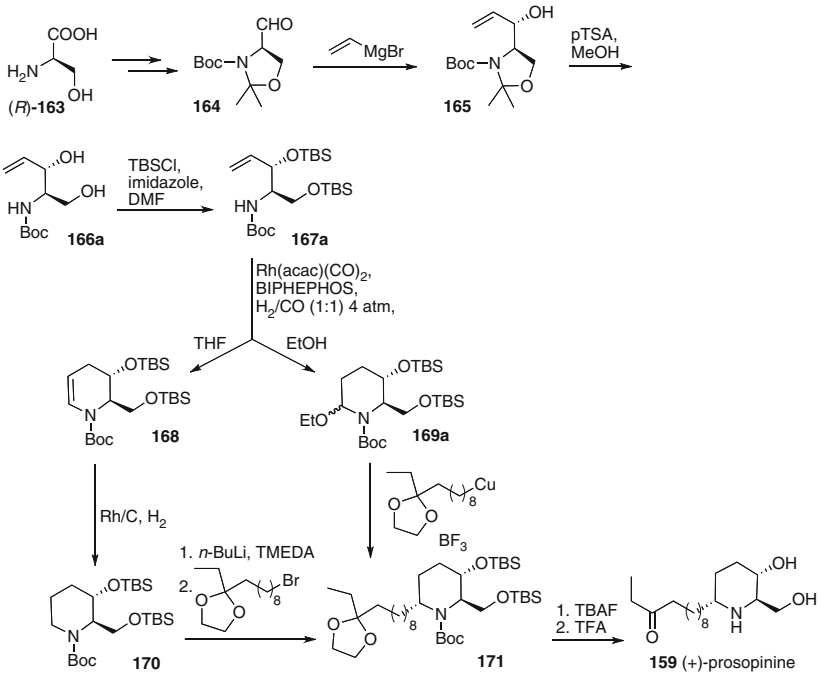
Scheme 49 Hydroformylation in piperidine alkaloid synthesis



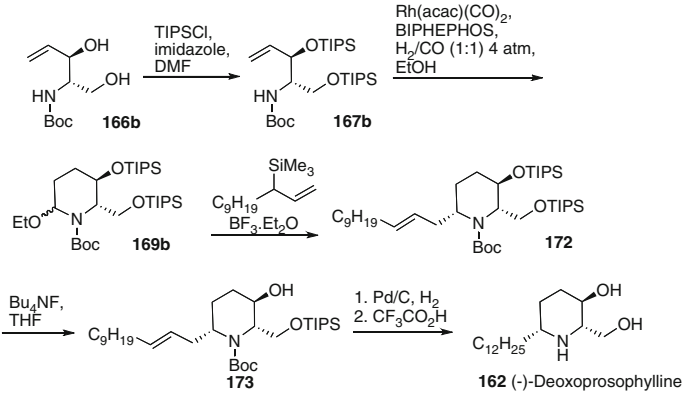
Scheme 50 Trisubstituted piperidine alkaloids

The synthesis of (+)-prosopinine **159** started with (*R*)-serine **163**, thus securing the *R* absolute configuration (Scheme 51). Serine was carried through to homoallylic amine derivative **167a**, which was subjected to hydroformylation in ethanol to give piperidine **169a**. Alternatively, hydroformylation of substrate **167a** in an aprotic solvent led to the formation of the enamine **168**. Both of these key intermediates were converted to the final natural product (+)-prosopinine **159** in good yields using different methods for attachment of the remaining side chain.

(−)-Deoxoprosophylline **162** was synthesized in a similar way, except that the TIPS protecting group was used and a Sakurai reaction was employed to introduce the final side chain (Scheme 52).

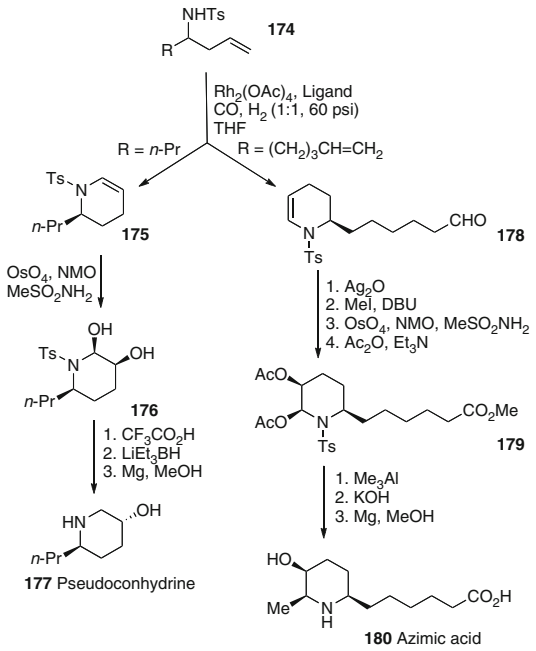


Scheme 51 Hydroformylation in prosopinine synthesis



Scheme 52 Hydroformylation in deoxoprosophylline synthesis

Recently, Bates and Kasinathan showed that incorporation of hydroformylation into organic synthesis could lead to an efficient and concise synthesis of natural products such as pseudoconhydrine **177**, isolated from *Conium maculatum* [94] and azimic acid **180**, isolated from *Azima tetracantha* L. [95, 96]. The tosyl-protected amine **174** obtained by the Vilaivan procedure [97] was subjected to hydroformylation to obtain the key enamine intermediates **175** and **178**. In the case of pseudoconhydrine synthesis (R = *n*-Pr), dihydroxylation under Upjohn conditions gave the all-*cis* diol



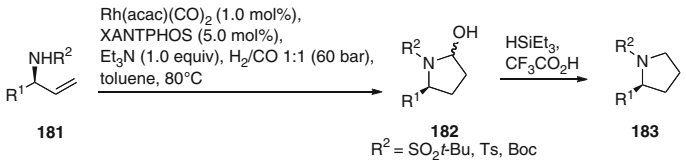
Scheme 53 Hydroformylation in hydroxypiperidine alkaloid synthesis

176. This could be converted to either the natural product **177** or the diastereoisomer. In the case of azimic acid **180**, double hydroformylation of sulfonamide **174** (R = pentenyl) occurred to give the aldehyde **178**. Once again using dihydroxylation, this could be taken through to the natural product **180** (Scheme 53) [98, 99].

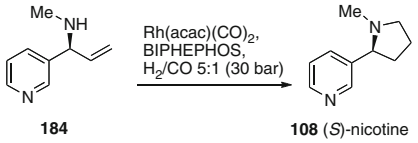
Helmchen et al. combined iridium-catalyzed [100–104] enantioselective allylic substitution with tandem hydroformylation-condensation in order to synthesize pyrrolidine alkaloids. They discovered that the outcome of the hydroformylation reaction was controlled by the substituent at nitrogen, and not by the substituent at carbon. This chemistry was used to achieve very short syntheses of (*S*)-nicotine **108** and the alkaloid 225C **187**. They showed that, in the case of hydroformylation of *N*-sulfonyl- and *N*-acyl-allylamines **181** under basic conditions, the hemiaminals **182** produced after cyclization of the intermediary aldehydes did not dehydrate to form enamines and could be isolated in good to excellent yields (Scheme 54) (this has only been observed previously with derivatives of the parent allylamine using Ph_3P as ligand, see [105]). The hydroxy group could subsequently be removed under Kursanov–Parnes conditions.

On the other hand, hydroformylation of *N*-alkylallylamine **184** resulted in situ reduction to give (*S*)-nicotine **108** (for other syntheses see [106–110]) in 61% yield and 99% ee without racemization (Scheme 55).

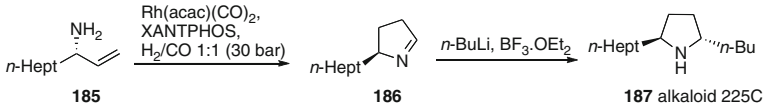
Further, hydroformylation of *N*-unprotected primary allylamine **185** produced cyclic imine **186**. Addition of an organolithium reagent to imine **186** gave alkaloid 225C **187** (for previous syntheses, see: [111–115]), a constituent of the venom of the fire-ant *Solenopsis fugax* (Scheme 56).



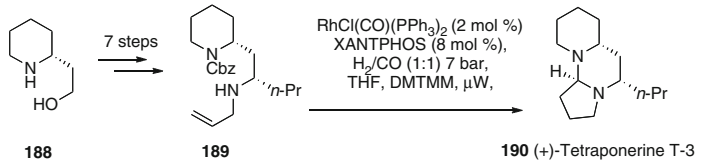
Scheme 54 Hydroformylation in pyrrolidine synthesis



Scheme 55 Hydroformylation in nicotine synthesis



Scheme 56 Hydroformylation in alkaloid 225C synthesis



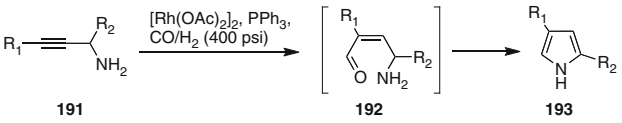
Scheme 57 Hydroformylation in tetraponerine synthesis

Condensation of the aldehyde generated by hydroformylation with two nitrogen nucleophiles was used in a synthesis of tetraponerine T-3 **190** ([116–125]; for related condensations, see [126]). Starting with the commercially available enantiomerically pure form of homopipecolic alcohol **188**, allylamine **189** was generated in seven steps. Hydroformylation of this compound under microwave conditions using an ionic liquid co-solvent gave (+)-tetraponerine T-3 **190** directly (Scheme 57).

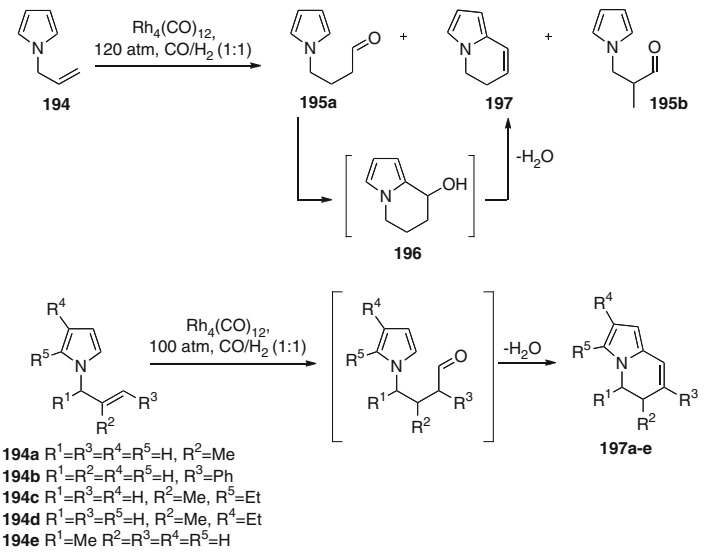
If systems with greater unsaturation are used, then aromatic nitrogen heterocycles may be formed. Campi et al. showed that rhodium catalyzed hydroformylation of readily available β-alkynylamines **191** gives 3-substituted or 2,4-disubstituted pyrroles **193** in good yields (Scheme 58) [127].

6.2 *Carbon Nucleophiles*

Lazzaroni et al. reported the first example of the one-pot synthesis of 5,6-dihydroindolizine **197** via rhodium-catalyzed hydroformylation of 1-allylpyrrole **194** (Scheme 59) [128]. 5,6-Dihydroindolizine **197** constitutes the basic skeleton



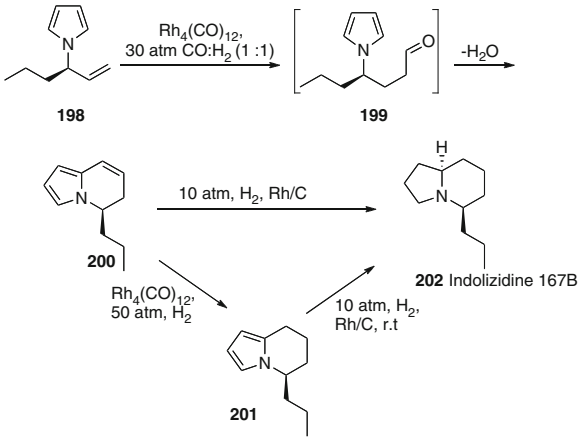
Scheme 58 Hydroformylation in pyrrole synthesis



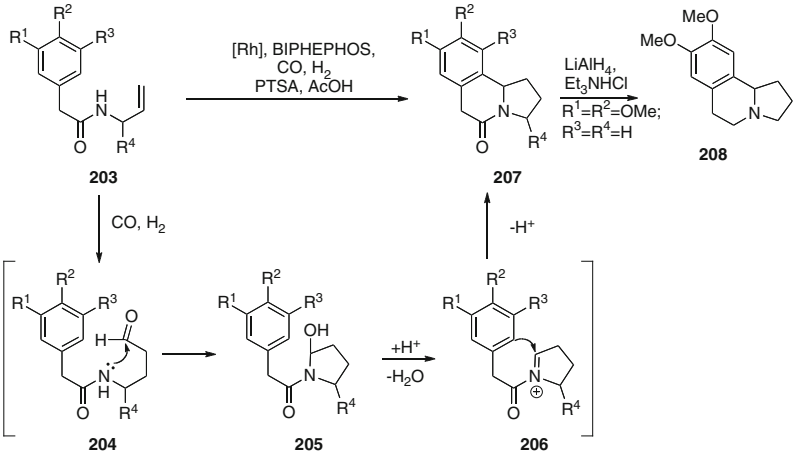
Scheme 59 Hydroformylation in indolizine synthesis

of many natural alkaloids ([129] and references cited therein; [130]). On hydroformylation of 1-allylpyrrole **194**, both the linear **195a** and the branched **195b** aldehydes were formed. The branched to linear aldehyde ratio ranged from 80:20 at 20°C to 59:38 at 100°C; only the linear regioisomer underwent intramolecular electrophilic aromatic substitution to give the intermediate alcohol **196,** which underwent dehydration to yield the 5,6-dihydroindolizine **197**. Interestingly, no extra ligands were added for these hydroformylation reactions. The reaction proved to be quite general, tolerating a wide range of substitution patterns [131].

This process was subsequently used as a key reaction in a synthesis of indolizidine 167B **202** (Scheme 60) [132]. Pyrrole **198** was synthesized from the amino acid D-norvaline [133] and subjected to hydroformylation to give an aldehyde **199** which underwent in situ intramolecular electrophilic substitution-dehydration to provide dihydroindolizine **200**. Replacement of the hydroformylation syngas with hydrogen resulted in conversion of dihydroindolizine **200** to 5,6,7,8-tetrahydroindolizine **201** without reduction of the pyrrole nucleus. On the other hand, use of Rh on carbon as a catalyst resulted in complete reduction to



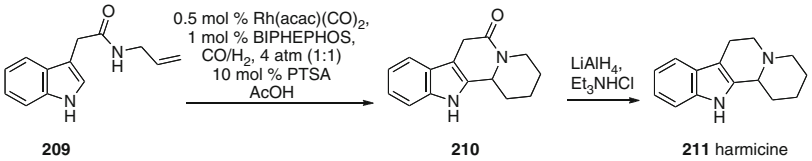
Scheme 60 Hydroformylation in indolizidine synthesis



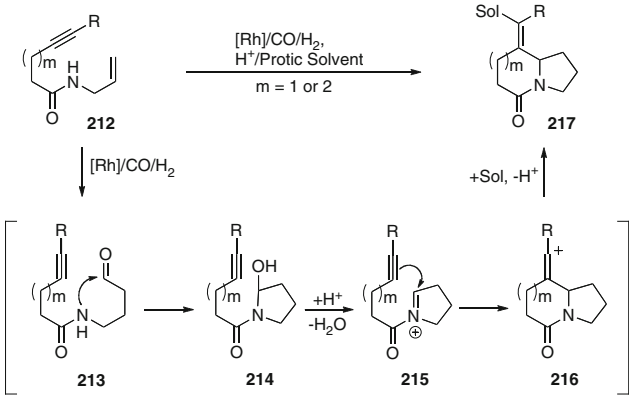
Scheme 61 Hydroformylation in crispine synthesis

(−)-indolizidine 167B **202**. The latter conditions could also be used on dihydroindolizine **201**, converting it directly to the natural product, indolizidine 167B **202**.

Other electron rich arenes may also be used to intercept the aldehyde formed by hydroformylation. Chiou et al. reported the hydroformylation of *N*-allylic amide of phenylacetic acid **203** to yield aldehyde **204** [134]. The aldehyde formed first condenses with the amide nitrogen to give an *N*-acyl iminium ion **206**. This condensation is followed by the second cyclization with the electron-rich arene to afford bicyclization product **207** (Scheme 61). This chemistry was used for the rapid construction of crispine A **208** (for isolation and cytotoxicity activity of crispine A see [135]; for syntheses of crispine A see [136–140]), isolated from



Scheme 62 Hydroformylation in harmicine synthesis

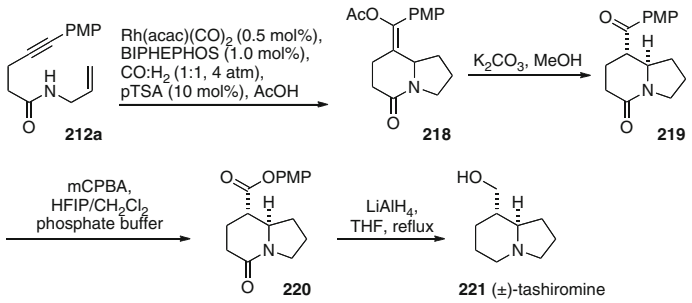


Scheme 63 Hydroformylation with interception by an alkyne

Carduus crispus, which is a potent antitumor agent. Use of an indole as the electron rich aromatic nucleophile resulted in a synthesis of the β-carboline alkaloid harmicine **211** (for isolation and anti-leishmania activity of harmicine see [141]; for synthesis see [138, 142–147]), isolated from *Kopsia griffithii*, which possesses strong antileishmania activity (Scheme 62).

An alkyne-mediated tandem Rh-catalyzed hydroformylation/double cyclization, for ready construction of indolizidine derivatives, has been devised as an extension of this concept [148]. The bicyclization process is initiated by Rh-catalyzed hydroformylation of amide **212** using a suitable ligand [71] to give the linear aldehyde **213** as the major isomer. The resulting aldehyde **213** undergoes spontaneous intramolecular cyclization to give hemiamidal **214** which, in the presence of an acid, dehydrates to yield *N*-acyliminium ion **215** [149]. *N*-Acyliminium ion **215** then undergoes a subsequent intramolecular cyclization with the alkyne moiety as a π carbon nucleophile, leading to the formation of the cation intermediate **216**, followed by solvent addition to give final bicyclic product **217** (Scheme 63).

Electron-donating groups on the phenyl moiety enhance the nucleophilicity of the triple bond moiety. Thus, a *p*-methoxyphenyl substituted alkyne **212a** was used in the synthesis of the naturally occurring indolizidine alkaloid (±)-tashiromine **221**, isolated from an Asian deciduous shrub *Maackia tashiroi* [150] (Scheme 64).



Scheme 64 Hydroformylation in tashiromine synthesis

7 Summary, Conclusions, Outlook

Hydroformylation is becoming increasingly accepted as a tool for the formation of a new carbon–carbon bond, and the introduction of the reactive aldehyde functional group. The use of specialized ligands, both to improve efficiency and control stereochemistry, the development of directed hydroformylation, and the possibilities opened up by tandem reactions are transforming this old reaction into a valuable new method.

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