ACS Catalysis

Review

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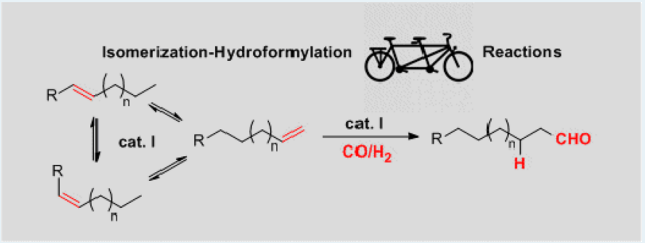
Isomerization−Hydroformylation Tandem Reactions

Marcelo Vilches-Herrera,[§] Lutz Domke,[†] and Armin Börner[§,†,*]

[§]Leibniz-Institut für Katalyse an der Universität Rostock e.V., A.-Einstein-Strasse 29a, 18059 Rostock, Germany

[†]Institut für Chemie der Universität Rostock e.V., A.-Einstein-Strasse 3a, 18059 Rostock, Germany

ABSTRACT: The metal-catalyzed isomerization−hydroformylation tandem reaction is of great importance for the production of linear aldehydes starting from internal olefins, but also, the shift of the double bond from a terminal position into the interior of an alkyl chain and the subsequent hydroformylation can be of interest. This review aims to summarize problems and achievements in this area under particular consideration of results published by the Leibniz-Institut für Katalyse (LIKAT) in the past two decades. A main focus is given to the variation of metals (Co, Rh, Ru, Pd, Pt, Fe) and phosphorus ligands used for the tandem reaction.

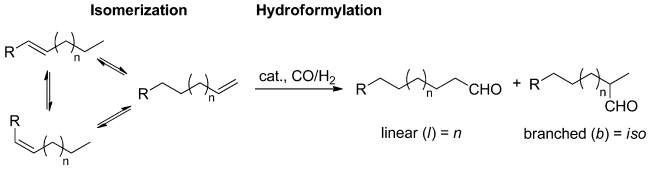


KEYWORDS: *tandem catalysis, isomerization, hydroformylation*

INTRODUCTION

Hydroformylation is the addition of carbon monoxide and hydrogen to olefins under formation of aldehydes (Scheme 1).[1]

Scheme 1. Interconnection between Isomerization and Final Hydroformylation of a Terminal Olefin



The reaction is catalyzed mainly by defined molecular metal complexes and constitutes one of the largest homogeneously catalyzed reactions in industry. In addition to the activity of the catalyst, its regioselecting power and, in the case of asymmetric reaction, its stereodifferentiating ability play a crucial role. The aldehydes formed not only are employed in bulk chemistry but also find increasing application as intermediates and final products in the pharmaceutical and aroma industries.[2] Of particular value for hydroformylation are transition metal complexes based on cobalt or rhodium, but also other metals, such as ruthenium, iridium, iron, platinum, or palladium, have been investigated.[3] In several cases, organic ligands, such as trivalent phosphorus compounds[4] or heterocyclic carbenes,[5] are used to tune the intrinsic catalytic properties of the metal.

In addition to the activity and chemoselectivity of the catalyst, the regioselectivity observed in the product aldehydes is one of the most important parameter to characterize the success of a hydroformylation reaction. This fact is expressed by the ratio linear/branched aldehyde ($l/b = n/iso$).

For most applications, the formation of isomeric product mixtures is not desired. Especially in bulk chemistry, *n*-aldehydes are the favored products. To achieve this goal, α-olefins are ideal substrates that can be converted with high n-regioselectivity into the corresponding terminal aldehydes. Under appropriate reaction conditions, the formation of isomeric, preferentially 2-aldehydes, is suppressed.[6] However, most technical feeds contain preferentially internal olefins, such as Raffinate I−III (all butene isomers)[7] or di-*n*-butene (mixture of isomeric C_8-olefins). In addition, with this starting material, the production of *n*-aldehydes is the favored target. This can be achieved only by shift of the olefinic double bond prior to the hydroformylation. The whole approach is termed isomerization−hydroformylation (Scheme 1). Relevant industrial units operate in a 10 000−100 000 tons scale.

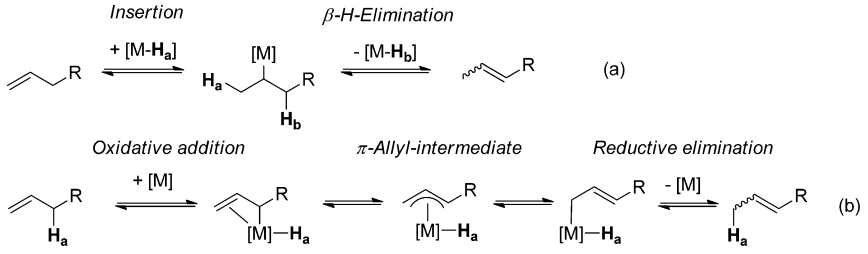
In a more general form, isomerization−hydroformylation can be defined as a process in which the net 1,2-addition of H−CHO takes place away from the original olefin. This definition includes not only the particular isomerization in favor of the terminal olefin, but also other migrations of the C═C double bond and subsequent hydroformylations.

Isomerization−hydroformylation reactions are assigned to so-called tandem reactions.[8,9] This approach allows the performance of more than one catalytic reaction in a single step; thus, disadvantages of separated reactions (e.g., treatment of sensible or thermodynamically less stable compounds, isolation, and purification of intermediates) are avoided. Moreover, in several cases, equilibria prior to or after the central reaction may have a beneficial effect on the rate, yield, and selectivity.[8]

Tandem reactions related to hydroformylation concern either the generation of the starting olefin or the transformation of the product aldehyde. Because of the taxonomy of Fogg and dos Santos for tandem catalysis, the hydroformylation catalyst must also be active in other catalytic events of the sequence.[9]

Received: March 2, 2014
Revised: April 11, 2014
Published: April 11, 2014

Scheme 2. Two Mechanisms of Metal Catalyzed Olefin Isomerization



Tandem reactions bearing a hydroformylation step have been summarized in the literature a few times.[1b,10] A most frequently cited article was written by Eilbracht et al. in 1999.[11] Updates were published in 2004 and 2006.[12] In 2003, Breit analyzed recent progress in stereoselective versions.[13] Recently, Behr and Vorholt reviewed tandem hydroformylation reactions with olefins derived from renewable resources.[14] The main focus of these reviews is usually given to catalytic transformations "beyond" the aldehyde, whereas reactions occurring prior to the hydroformylation are neglected or mentioned periferally.

In isomerization–hydroformylation, the question of regioselectivity is addressed twice: first, regioselective isomerization of the double bond and, second, regioselective hydroformylation. Since the discovery of hydroformylation 75 years ago,[15] mostly the second reaction was in the focus of academic research. Meanwhile, a detailed understanding of how to control the n-regioselective hydroformylation of a terminal olefin has been developed, although sometimes, small differences in ligand and substrate structure may produce sharply different catalytic profiles.[16,17] The situation in isomerization–hydroformylation is different because here, an enhanced number of preequilibria has to be considered. This situation leads to a hardly manageable complexity. Nevertheless, in the past two decades, progress has been witnessed, which reveals that knowledge accumulated in the highly n-regioselective hydroformylation of 1-olefins can be adapted to run successfully the isomerization–hydroformylation.[18] This is perspicuous because both reaction types have the last step in common. Therefore, a review on isomerization–hydroformylation should also address some basics of nonisomerizing n-regioselective hydroformylation.

Several contributions in this respect have come from the Leibniz Institut für Katalyse (LIKAT) in Rostock. Most important results will be summarized herein, together with the main achievements reported by other research groups.

GENERAL ASPECTS

Isomerization of olefins by transition metal complexes presents one of the most important goals in organometallic chemistry.[19,20] For the topic considered herein,[21] two principal mechanisms can be differentiated (Scheme 2): (a) metal hydride addition–elimination mechanism (alkyl mechanism)[22] or (b) reaction via a π-allyl metal hydride intermediate (allyl mechanism).[23]

The crucial difference between them is that the former mechanism represents a net 1,2-hydrogen shift, and the latter constitutes a net 1,3-migration of hydrogen. For isomerization occurring via the first mechanism, a cocatalyst, for example, hydrogen or acids, is required for the generation of the intermediate metal hydride.[24] Particularly active are those transition metal hydrides based on Co(I), Rh(I), Pd(II), and Pt(II), which are also widely used in hydroformylation. The reaction via π-allyl metal intermediates seems to be less common, but accounts for metal catalysts, which do not possess hydride ligands, such as $Fe_3(CO)_{12}$[23] or $PdCl_2(C_6H_5CN)_2$.[25,26] Sometimes photocatalytic activation is required. It appears that for rhodium catalysis mechanism, the former is of greater relevance.[27] With cobalt catalysts, a pressure dependency of the mechanism has been concluded by Pino et al.[27] Moreover, Orchin and Rupilius suggested for some cases a mixed σ–π-interconversion pathway.[28]

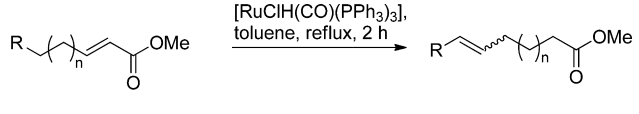
Product composition after thermal olefin isomerization depends on reaction conditions, catalysts, and olefinic substrate. Usually, high temperatures stimulate migration of the double bond.[29] Diminishment of repulsive interactions between catalysts and coordinated substrate forces generation of the thermodynamically favored intermediates or products.[30] Therefore, the application of organic ligands with varying steric bulk can be advantageous.

With nonfunctionalized terminal olefins, the formation of internal olefins is favored. Less than 5% of the terminal olefins may be present in the thermodynamic equilibrium. Slow isomerization in comparison with the subsequent hydroformylation may lead to a continuous erosion of the regioselectivity during the reaction.[31] (*E*)-Olefins are more stable than *Z* isomers; therefore, double bond migration can commence with an *Z*/*E*-isomerization step.[32]

Aryl substituents or functional groups in the olefin can strongly influence the direction of the double bond shift. Preferred isomerization of the olefinic double bond toward the neighborhood of aryl substituents or functional groups (such as keto groups; cyano, ester or carboxylic acid groups) may be counterproductive for the subsequent hydroformylation step because in the presence of syngas, hydrogenation of the olefin becomes a dominant side reaction.[33] This holds likewise for the conjugation of isolated double bonds, which is, for example, mediated by rhodium[34] or bimetallic platinum catalysts.[35] Formed 1,3-butadienes are less prone to hydroformylation.[36,37] Interestingly, Mori and co-workers achieved deconjugation of α,β-unsaturated esters in the presence of a homogeneous ruthenium catalyst (Scheme 3).[38]

Transition-metal-catalyzed isomerization and hydroformylation are competing processes. They can be mediated by the same catalyst and proceed via some common intermediates (Scheme 4). Of pivotal importance for isomerization as well as for hydroformylation is the generation of regioisomeric σ-alkyl–metal intermediates formed by addition of the metal

Scheme 3. Deconjugation of α,β-Unsaturated Esters



R = OTBDPS, $(Bu_3Sn)_2CH$

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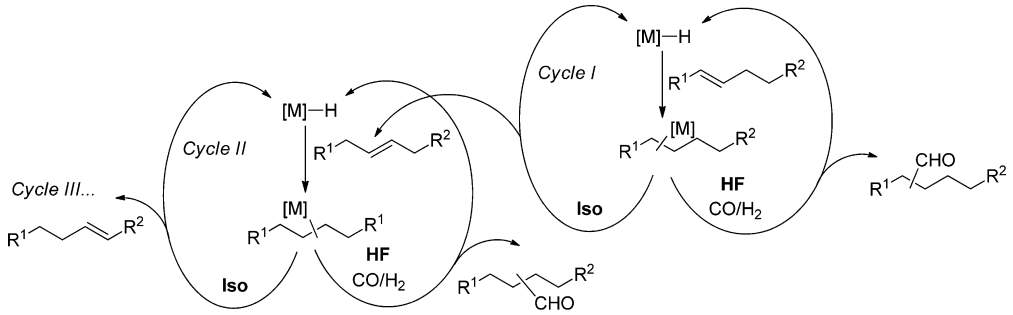
Scheme 4. Simplified Mechanisms for Two Cycles of Isomerization−Hydroformylation Tandem Reaction[a]



[a]HF = hydroformylation; Iso = isomerization; only the most important relationships are depicted; equilibria are not indicated.

hydride to the starting olefin in cycle I. These intermediates can be in equilibrium with the starting 1-olefin but also with the isomerized 2-olefin. In this way, cycle II is entered. Repetition of this mechanism leads to the 3-olefin, etc. in a "chain running mechanism". Electron-pushing alkyl groups and less bulky ligands at the metal center favor the formation of branched metal alkyl intermediates.[39] In contrast, steric interactions between catalyst and substrate support the formation of terminal metal alkyl complexes.[40]

Overwhelming evidence has been accumulated that with most metal catalysts, isomerization is reversible.[41] The isomerization rate is dependent on the substituents of the substrate.[42] Thus, with (*E*)-4-octene, the migration of the double bond to the terminus is ∼3.5 times slower than the isomerization of the terminal double into the carbon chain.[43]

In the presence of CO, each isomerization cycle can be interrupted by the formation of the corresponding metal−acyl complexes, which are finally converted with hydrogen into aldehydes (Scheme 4).[44] The selective management of these competing mechanisms determines the number and ratio of regioisomeric aldehydes. Unfortunately, because of the huge number of equilibria, which influence these transformations in a sometimes unpredictable manner, until now, quantitative forecasts have not been possible.

An increase in the steric hindrance at the double bond deactivates the olefin toward hydroformylation (2-pentene > 3-hexene > 4-octene);[45] however, symmetric internal olefins, such as (*E*)-4-octene, give a higher yield of *n*-aldehyde than nonsymmetric (e.g. 3-octene) because of the possibility of double bond migration to both ends. It should be noted that hydroformylation of α-olefins as well as of β-olefins can lead to the same 2-aldehydes; however, only with β-olefins can 3-aldehydes also be formed.

Functional groups can be used for directing the regioselectivity of the C−C bond formation. Recent work by Breit and Reek gave evidence that in particular, carboxylic acid groups are powerful regiodirecting groups in supramolecular catalyst−substrate assemblies, which allows even the iso-selective hydroformylation of both internal and terminal olefins.[46]

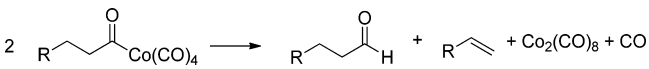
Irrespective of these particularities, some conclusions are possible, which may allow a better understanding of the complex interrelations.[1b,41] It is known that metal−acyl complexes, which derive from the insertion of CO into the metal−alkyl bond, are mostly irreversibly converted into aldehydes. Therefore, all effects that support this step favor hydroformylation over isomerization. Usually, an excess of CO inhibits isomerization. Weakening of the M−CO bond facilitates the dissociation and supports the subsequent insertion into the M−alkyl bond. Especially organic ligands (e.g., trivalent phosphorus ligands) at the metal center can promote the migration due to electronic effects (trans effect).

Insights into the mechanism have been concluded from H_2/D_2 scrambling experiments[47] or by using para-hydrogen-induced polarization (PHIP).[48] Elucidation has been likewise obtained by use of chiral olefins with stereogenic carbon atoms close to the double bond, which may racemize in the course of the isomerization.[49]

In recent years, numerous attempts have been published to correlate the geometry of catalyst/substrate intermediates with the n/iso ratio of product aldehydes derived from the hydroformylation of 1-olefins.[50] Conclusions are based mainly on spectroscopic measurements or chemical calculations.[51] Especially, Tolman's cone angle (θ)[52] and the natural bite angle (β_n),[50] respectively, are used to estimate the space-filling properties of a ligand. These studies refer preferentially to phosphorus-modified rhodium catalysts and 1-olefins as substrates, but they can contribute to a better understanding of the isomerization−hydroformylation, as well.[53,54]

Apart from these more simplified assumptions about the course of isomerization−hydroformylation, some peculiarities should be taken into consideration. Thus, olefins can also be formed by disproportionation of a cobalt−acyl complex, leading to the impression that isomerization has taken place (Scheme 5).[28]

Scheme 5. Disproportionation of a Co−Acyl Complex Under Formation of a Terminal Olefin



Finally, a hydroformylation−decarbonylation−hydroformylation sequence can also be responsible for an unexpected ratio of aldehyde regioisomers. Brookhart and co-workers observed by means of NMR studies the migration of the formyl group when *n*-butanal was heated in the presence of a Cp*-rhodium catalyst (Scheme 6).[55] Within 8 h, a 1:1 mixture of both isomers was observed. With *n*-pentanal as the substrate, all regioisomers yielded under these conditions.

COBALT CATALYSTS

Cobalt-catalyzed hydroformylation originates back to the discovery of hydroformylation by O. Roelen in 1938. Today, next to rhodium, cobalt is still the most widely used metal in this respect. Since the pioneering studies by Heck and Breslow,[56] until now, numerous reports have been published

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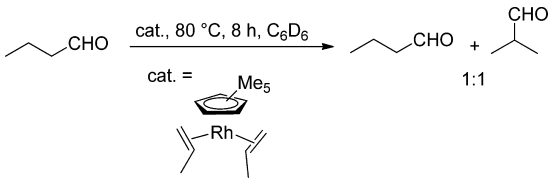
Scheme 6. Rhodium-Catalyzed Isomerization of Aldehydes



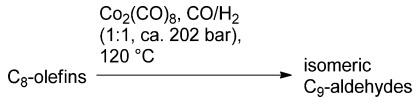
dedicated to details of the mechanism, such as catalysts, catalytic intermediates, and equilibria.[57] Irrespective of these investigations, several open questions remain still to be answered.

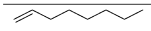
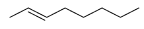
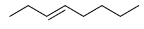
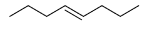
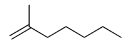
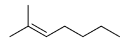
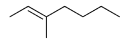
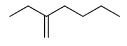
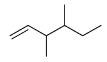
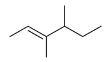
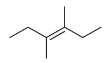
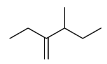
As emphasized in most textbooks, unmodified cobalt catalysts isomerize internal and terminal olefins at comparable reaction rates. The reaction proceeds in a "chain-running" mechanism to give all possible isomers. In the hydroformylation, a general tendency for the formation of *n*-aldehydes independent of the starting olefins used is observed, which accounts for a strong kinetic preference for the irreversible generation of the (*n*-alkyl)acyl-Co intermediate[58] and its conversion into aldehydes.[47,59] These more general statements are derived mainly from large-scale technical processes (BASF, Exxon),[60] which operate at the high temperatures (120−175 °C) and high CO pressure (270−300 bar) necessary for the generation and stabilization of the catalytically active cobalt hydrido complex.[61] In this manner, 60−70% *n*-aldehydes can be produced from higher, preferentially terminal, alkenes. Modification of the metal with phosphine ligands (Shell process)[60] improves the thermal stability of the catalyst and increases the n-regioselectivity to 75−90%; however, this modification affects the hydroformylation activity, and higher temperatures are required (150−190 °C). Alcohols are preferentially formed as a result of the enhanced hydrogenation activities of $[HCo(CO)_3PR_3]$.

In an earlier study, Haymore et al. investigated the aldehyde distribution observed in the hydroformylation of a technical mixture of linear and branched C_8-olefins (*n*-octenes, 2-methylheptenes, 3-methylheptenes, 3,4-dimethylhexenes, 2,4-dimethylhexenes) with an unmodified Co catalyst.[62] Typical conversions and yield ratios are given in Table 1. Both parameters only slightly differed when *Z*- or *E*-olefins were employed. The preference for the C−C-bond formation at the terminus of any olefin is obvious. This tendency is forced by branching of the olefin. Internal olefins give a lower yield of terminal aldehydes.

In general, the regioselectivity of the hydroformylation with unmodified Co catalyst is strongly affected by temperature and CO partial pressure, whereas catalyst concentration and H_2 partial pressure are less important.[47] When nonprotic solvents (toluene, methyl orthoformate, diethyl ether, 1,4-dioxane) were varied, almost no effect on the regioselectivity was noted.[63] By application of terminal olefins, an increase in the CO partial pressure diminishes the rate of isomerization.[64] Under high pressure, even *Z*/*E*-isomerization of internal olefins is inhibited. Pino explained the CO effect by the assumption of the fast formation of $[HCo_3(CO)_9]$ in a solution containing $[HCo(CO)_4]$ and its precursor $Co_2(CO)_8$ under hydrogen (Scheme 7).[65] $[HCo_3(CO)_9]$ reacts with hydrogen to give $[HCo(CO)_3]$.[66] This $16e^-$ complex is active in isomerization. Clearly, $[HCo(CO)_3]$ is likewise considered a hydroformylation catalyst. This at first glance contradictory statement can be clarified by the assumption of a prolonged lifetime of the

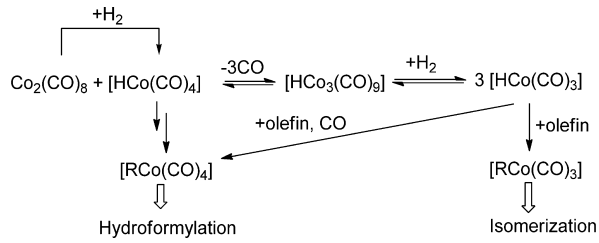
Table 1. Conversion and Product Distribution in the Hydroformylation of Isomeric C_8−Olefins with an Unmodified Cobalt Catalyst



Olefin	Conversion	Position of the aldehyde group [%]							
	[%]	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
	66	65.5	13.8	3.6	2.3	1.6	1.3	3.0	8.9
	55	62.0	21.4	9.9	6.7	-	-	-	-
	52	56.7	17.8	13.0	12.5	-	-	-	-
	52	56.2	17.0	11.0	15.8	-	-	-	-
	79	78.7	3.8	0.1	1.6	2.2	3.5	10.1	-
	68	63.9	1.2	0.2	3.3	4.3	6.9	20.2	-
	51	72.4	3.9	0.5	0	0.6	1.8	5.6	-
	47	17.3	1.2	2.9	0.1	1.0	2.2	7.4	-
	71	96.3	2.5	0	-	-	-	-	-
	44	87.6	3.4	0.2	8.8[a]	-	-	-	-
	24	29.8	1.3	1.2	67.7[a]				
	58	11.8	0.4	2.1	85.7[a]				

[a]Yield of 3-ethyl-4-methylhexanal.

Scheme 7. Competition between Isomerization and Hydroformylation in Dependence on the CO Pressure



subsequently formed electronically unsaturated complex $[RCo(CO)_3]$ in the absence of CO. This facilitates the reverse β-hydride elimination under formation of a thermodynamically more stable internal olefin. In contrast, enhanced CO pressure generates $[RCo(CO)_4]$, which is a direct precursor of the aldehyde.

This hypothesis is in agreement with later work of Jiao, who calculated the whole mechanism of the cobalt-catalyzed hydroformylation of propene.[67] It was also found that the process leading to isomeric Co−alkyl complexes is reversible.

In comparison with rhodium-catalyzed hydroformylation, the effect of organic ligands on the cobalt-catalyzed hydroformylation is less pronounced. Moreover, a desired regiodirecting effect strongly depends on the equilibrium between modified and unmodified catalyst.

dx.doi.org/10.1021/cs500273d | ACS Catal. 2014, 4, 1706−1724

Slaugh and Mullineaux compared the effect of different monodentate phosphine ligands on the hydroformylation of 1-pentene.[68] In general, higher yields of linear aldehydes were noted with basic trialkylphosphines in comparison with PPh_3,[69] but with the latter, hydrogenation was almost suppressed. Replacement of phosphines by arsines decreased the n-regioselectivity.[70] Apparently, PBu_3 with a cone angle θ of 136° and a pK_a of 8.4 best meets the steric and electronic requirement for *n*-regioselective hydroformylation.[71] The following order of ligands forcing the formation of *n*-aldehydes/*n*-alcohols can be derived from these studies:

$$PBu_3 > PEt_3 \approx PCy_3 > PPh_3 > AsPh_3$$

To find a less volatile and more stable phosphine than Bu_3P, in 1968, Shell suggested phosphabicyclononanes ("phobanes") (Scheme 8).[72] Relevant cobalt catalysts are characterized by a

Scheme 8. Phosphine Ligands for Cobalt Catalyzed Hydroformylation

Phobanes

R = $C_{20}H_{41}$ (Shell); H, C_2H_5, C_5H_{11}, $C_{10}H_{21}$, $C_3H_6NMe_2$, C_6H_{11}, Ph (Bungu)

LIM-ligands

R = H, C_5H_{11} (LIM-5), $C_{10}H_{21}$ (LIM-10), $C_{18}H_{37}$ (LIM-18), C_3H_6CN

reduced hydrogenation activity toward the olefin.[73] In the Co-catalyzed hydroformylation of 1-dodecene using a mixture of both diastereomers (R = $C_{20}H_{41}$) at 183−185 °C, 85 bar syngas (CO/H_2 = 1:2), the corresponding alcohol was obtained in 87% yield and with a linearity of 89%. This approach was extended by Bungu and Otto using related bicyclic trialkylphosphines.[74] Also with these ligands, high n/iso selectivities of 85−90% were noted, which are slightly above the regioselectivity obtained with Bu_3P (81%). The cone angles of phobane ligands were determined in the range from 159 to 165°. Crause et al. synthesized "LIM ligands" from enantiopure limonene.[75] The lowest n-regioselectivity (54%) was induced using the catalyst bearing LIM−C_3H_6CN. LIM-5 was most regioselective (71%). A comparison of diastereomeric ligands showed almost no effect.[76] However, branching of the long chain alkyl substituent in LIM ligands decreased the regioselectivity.

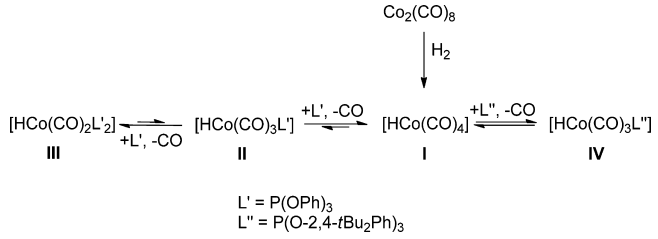
With chelating diphosphines of the type $Ph_2P(CH_2)_nPPh_2$, the regioselectivity dropped in the following order, which corresponds to the diminution of the chelate ring size:[68]

$$n = 5 \approx n = 4 > n = 2$$

By application of diphosphine ligands, in cobalt-catalyzed hydroformylation, an "arm-off mechanism" has to be taken into consideration, which may hamper the beneficial creation of steric congestion around the metal center, as seen later with corresponding rhodium or platinum catalysts.

Complex $[HCo(CO)_2\{P(OPh)_3\}_2]$ (**III**, Scheme 9), which was prepared starting from $Co_2(CO)_8$ by treatment with H_2 and subsequent addition of two phosphite ligands to **I**, was able to isomerize 1- into 2-pentene.[77] Surprisingly, the corresponding complex $[HCo(CO)_3\{P(OPh)_3\}]$ (**II**), which was observed only in small amounts in the equilibrium, displayed a poor hydroformylation activity. By application of the sterically more

Scheme 9. Formation of Phosphite Based Cobalt Complexes

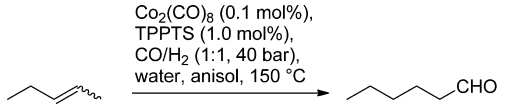


demanding ligand $P(O\text{-}2,4\text{-}t\text{Bu}_2\text{Ph})_3$, the complex **IV** bearing only one phosphite could be selectively generated,[78] but this complex formed a very sluggish hydroformylation catalyst. This is a remarkable difference from rhodium-catalyzed hydroformylation, in which such monophosphites induce superior activities.

Some investigations were carried out to run the cobalt-catalyzed hydroformylation of long-chain olefins in aqueous biphasic systems. Martin's group investigated the reaction of a technical decene mixture in an aqueous two-phase system (60−200 bar, 150−180 °C).[79] As ligands, TPPTS [tris(natrium−*m*-sulfonatophenyl)phosphine] or phosphines bearing sodium alkylphosphonate or lithium alkylsulfonate groups were screened. At higher temperatures and syngas pressure, the results resembled those obtained with the unmodified cobalt system, indicating the instability of the phosphine-modified catalyst.

Beller and Krauter found that by the effect of a Co/TPPTS catalyst on a mixture of isomeric 2-pentenes, almost exclusively aldehydes were formed at a syngas pressure of 30−100 bar and 130−150 °C (Scheme 10).[80] The n/iso regioselectivity was about 2/1.

Scheme 10. Isomerization−Hydroformylation of Isomeric 2-Pentenes in an Aqueous Two-Phase System



Higher temperatures and lower syngas pressures decreased the regioselectivity. The catalyst could be recycled from the aqueous biphasic system and showed almost no loss of regioselectivity within four consecutive runs.

The addition of other metals to the heterogeneously cobalt-catalyzed reaction can have a beneficial effect on catalytic activity as well as regioselectivity. For example, small amounts of ruthenium added to a carbon-supported cobalt catalyst (Co/AC) increased activity as well as n/iso selectivity.[81] The effect was rationalized by the high dispersion and reducibility of supported cobalt. Together with ruthenium added, small particles of an unbalanced alloy were formed. These particles keep more CO in a nondissociative state and lower the surface hydrogen pressure. This was in contrast to related but uniformly distributed Pt−Co or Pd−Co alloys. Activity and regioselectivity increased with an increased Ru loading.

It should be noted that some metal catalysts can initiate 1,2-sigmatropic rearrangement, which may lead to a further modification of the olefin serving as substrate of the hydroformylation. A typical example is the isomerization−

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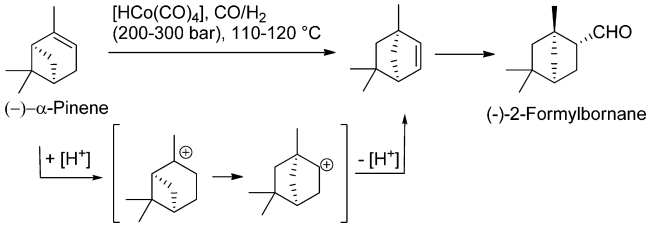
hydroformylation of α-pinene with an unmodified cobalt catalyst (Scheme 11).[82] In strong contrast to rhodium, the cobalt catalyst afforded 2-formylbornane. The 1,2-sigmatropic rearrangement was explained by the acidic nature of [HCo(CO)$_4$].

Scheme 11. 1,2-Sigmatropic Alkyl Shift Prior to Hydroformylation

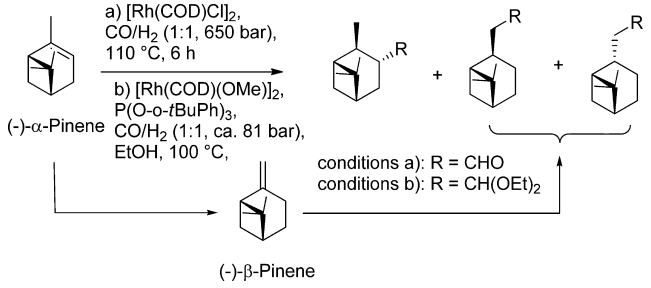


RHODIUM CATALYSTS

Beginning in the 1950s, the first hydroformylation experiments were conducted with unmodified metal clusters $Rh_2(CO)_8$, $Rh_4(CO)_{12}$, and $Rh_6(CO)_{16}$ or later with the mononuclear complex [HRh(CO)$_4$].[83] In strong contrast to unmodified cobalt catalysts, rhodium congeners show poor regiodiscriminating ability and usually give equal amounts of *n*- and *iso*-aldehyde when a terminal olefin is used as the substrate. This difference has been rationalized by a larger size of the metal center in [HRh(CO)$_3$] in comparison with [HCo(CO)$_3$]; therefore, steric effects on the coordinated olefin are less pronounced.[84]

Lazzaroni et al. found that in the presence of $Rh_4(CO)_{12}$, isomerization of 1-hexene into preferentially 2-hexene takes place only at higher temperatures.[85] Sterically constrained olefins can easily undergo isomerization into a less congested structure. Dos Santos and Gusevskaya observed in the hydroformylation of α-pinene at 110 °C, in addition to (+)-3-formyl pinane, two diastereomers of 10-formyl pinane (Scheme 12).[86] The latter were formed as a result of the

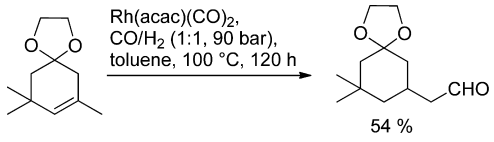
Scheme 12. Isomerization−Hydroformylation of α-Pinene



rearrangement of the α-isomer to give the better accessible exocyclic double bond in β-pinene. The reaction could be likewise run under much milder conditions as an isomerization−hydroformylation−acetalization reaction in the presence of a rhodium phosphite catalyst to give 20−40% yield of the terminal acetals.[87] The isomerization was less significant at high ligand concentrations.

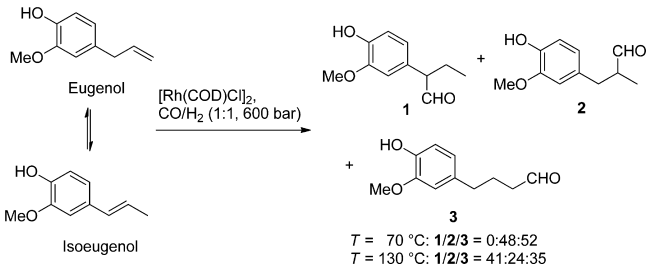
A related migration of an endocyclic double bond was found prior to the hydroformylation of β-isophorone acetal (Scheme 13).[88] As a major product, the exocyclic aldehyde was formed.

Scheme 13. Isomerization−Hydroformylation of β-Isophorone Acetal



The isomerization to a thermodynamically more stable internal olefin can be supported by the structure of the substrate. Thus, it is known that with an appropriate isomerization catalyst, 2-aryl propenes can be in equilibrium with 3-aryl propenes. A typical example is the temperature-dependent isomerization−hydroformylation of eugenol, which preferentially gives either the terminal aldehyde **3** or the branched 1-aldehyde **1** (Scheme 14).[89]

Scheme 14. Regioisomeric Hydroformylation of Eugenol in Dependency on the Temperature



A breakthrough in the rhodium-catalyzed hydroformylation was achieved by Osborn and Wilkinson, who discovered by application of PPh_3-modified rhodium complexes a dramatic improvement of not only activity but also of regiodiscrimination yields.[90] In the hydroformylation of 1-alkenes with [RhCl(CO)(PPh_3)$_3$] at 60 °C, a ratio of n/iso = 2.7 was noted. Addition of an excess of PPh_3 to the reaction with [HRh(CO)(PPh_3)$_2$] at room temperature improved this ratio up to 20. At higher temperatures, the regioselectivity deteriorated. Ph_3P induced superior n/iso selectivities in the hydroformylation of 1-dodecene in comparison to Ph_3As.[91] Usually, with P-modified rhodium catalysts, an increase in the CO partial pressure lowers the regioselectivity in the hydroformylation of α-olefins because of the competition between CO and the P-ligand for the rhodium center (Scheme 15). This behavior is in contrast to the hydroformylation with [HCo(CO)$_3$]/[HCo(CO)$_4$] (see Scheme 7).

In an attempt of hydroformylation of (*Z*)- or (*E*)-2-alkenes at 25 atm syngas pressure and 100 °C, exclusively branched

Scheme 15. Competition between Isomerization and Hydroformylation in Relation to Dependence on the CO Partial Pressure in the Hydroformylation of Terminal Olefins

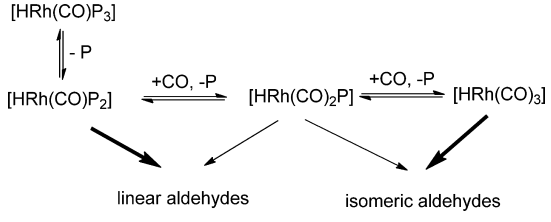


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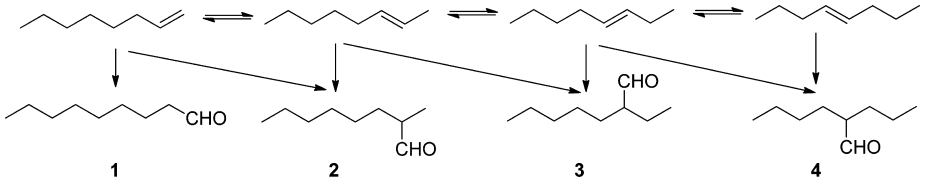
Table 2. Product Formation in Dependence on the Syngas Pressure[a]



		selectivities (%)			
substrate	pressure (MPa)	1	2	3	4
1-octene	6.4	54.5	37.0	6.3	2.2
1-octene	500	51.8	48.1	0.1	0.0
4-octene	7	0.9	12.7	31.3	55.2
4-octene	500	0.3	5.2	26.1	68.4

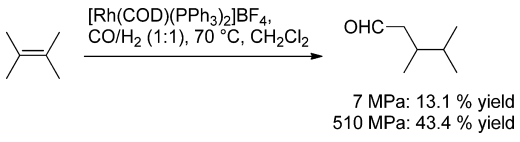
[a]Conditions: $[Rh(COD)(PPh_3)_3]BF_4$ (2 mol %), 70 °C, CH_2Cl_2, 16 h.

aldehydes were formed, which demonstrates the low isomerization activity of rhodium catalysts with monodentate phosphine ligands.[90b] In particular, basic trialkylphosphines suppress isomerization.[69] Replacement of PPh_3 by TPPTS leads to a higher n/iso ratio as a result of an improved stability of the $Rh(CO)(TPPTS)_3$ complex.[92] These findings provided the chemical basis for the development of the technical "low-pressure oxo (LPO)" processes conducted by Ruhrchemie/Rhône-Poulenc (now Oxea), UCC, BASF, Evonik Industries, and Mitsubishi for the hydroformylation of unfunctionalized olefins of different chain lengths.[60,93]

Albers et al. analyzed the pressure effect on the hydroformylation of 1- and 4-octene with $[Rh(COD)(PPh_3)_2]BF_4$ at 70 °C (Table 2).[94] As expected, with the terminal olefin as substrate, at low pressure, *n*- and *iso*-aldehyde **1** and **2** were formed in a ratio of 1.6/1. Because of some isomerization, the other branched aldehydes **3** and **4** were also detected in descending amounts. An extremely high syngas pressure of 500 MPa completely suppressed double bond migration, and *n*-nonanal and 2-methyl octanal were formed in almost equal quantities.[95] This result nicely illustrates the poor ability of the catalyst to discriminate between the 1- and 2-position of the terminal double bond. With 4-octene as substrate, at low pressure, isomerization also played a significant role. The highest yield of 4-formyl octane (**4**), which derives from the C−C bond formation in the C_4/C_5 position of 4-octene, was observed at 500 MPa. It is noteworthy that aldehydes **2** and **3** were also yielded. These products require the prior isomerization of 4-octene into the less thermodynamically stable olefins, which accounts for kinetic control. This result is in contrast to the reaction with 1-octene under the same conditions.

The hydroformylation of 2,3-dimethyl-2-butene is also pressure-dependent.[94] At low pressure, only a poor yield of 3,4-dimethyl-pentan-1-al was observed (Scheme 16). At 510 MPa, the yield of this terminal aldehyde increased by a factor of ~3.

Scheme 16. Isomerization−Hydroformylation of 2,3-Dimethyl-2-butene



A breakthrough in the n-regioselective hydroformylation was achieved by the application of bidentate diphosphines, such as BISBI[96] or NAPHOS[97] (Scheme 17). In general, the stability of the corresponding metal complexes benefits from the chelate effect. Therefore, the competition with CO for coordination at the metal is less important in comparison with monodentate phosphines. Usually, these ligands induce excellent yields of linear aldehydes in the hydroformylation of terminal olefins.

It is clear that this feature was likewise tested in the isomerization−hydroformylation of internal olefins. Beller et al. replaced the P-phenyl groups in NAPHOS with fluoro-substituted aryl groups (IPHOS).[98] This electronic modification enhanced the n-regioselectivity in the hydroformylation of internal olefins in comparison with the parent ligand (n/iso = 91/9 for 2-pentene; n/iso = 86/14 for 2-octene; n/iso = 66/34 for 4-octene; TOFs = 60−425 h^{-1}). The results correlate well with earlier studies with α-olefins, which showed an enhanced ratio of linear to branched aldehydes with less basic phosphines.[99]

Xantphos is the generic name of a class of diphosphines consisting of numerous individuals suggested by van Leeuwen's group.[50b−d,100] These ligands are of particular value for the study of structure−activity/regioselectivity relationships and allowed, for the first time, a more rational design of catalysts.[29,101] Variation of X in the middle ring of the xanthene structure allows the adjustment of bite angles in the range of 102−121° at constant electronic effects. The natural bite angle (β_n) is defined as the preferred chelation angle determined by the constraints of the ligand backbone. A wide bite angle forces isomerization of internal olefins and fixes the terminal double bonds.[101] Replacement of the PPh_2 groups by dibenzophospholyl- or phenoxaphosphino groups further extended the family of large bite angle diphosphines with angles until β_n was 131°[102] and allowed improvement in the n-regioselectivity in the hydroformylation of (*E*)-2-octene, (*E*)-4-octene, and 2-pentene by a factor of 10.[103] Regioselectivities sometimes even exceeded those obtained with terminal olefins as substrate. Interestingly, conversion and yield of aldehyde were also superior as a result of application of some of these ligands. In the best cases, TOFs of 100−400 h^{-1} could be achieved. Ligands with long alkyl groups in the periphery of the xanthene backbone (R^1) have been used for the hydroformylation of Raffinate II[7] (CO/H_2 = 1:1, 25 bar; 115 °C, 72 h) to yield more than 70% conversion of isomeric valeraldehydes with n/iso ratios by up to 93:7.[104]

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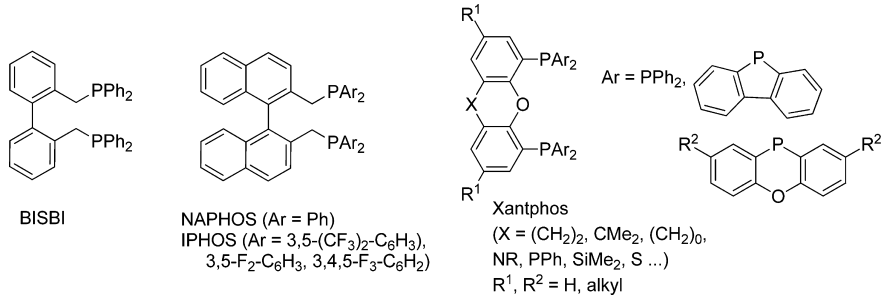
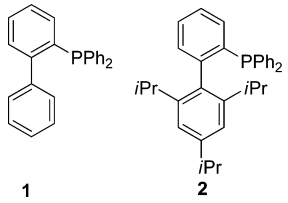
Scheme 17. Large-Bite-Angle Diphosphines Suitable for Isomerization−Hydroformylation



As seen, an increase of the steric bulk caused by the ligand may contribute to the regiodiscriminating ability of the catalyst; however, the subtle balance between this desired effect and the propensity of the ligand for coordination to the metal should be taken into consideration. Recently, van Leeuwen and co-workers pointed to the fact that certain biarylmonophosphines, which are successfully used as ligands in other transition metal catalyses may not coordinate to rhodium, even under rather smooth hydroformylation conditions.[105] Thus, rhodium catalyst precursors treated with phosphines **1** and **2** (Scheme 18)

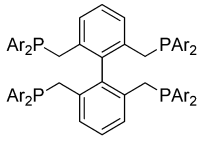
Scheme 18. Biarylmonophosphines with Large Cone Angles Which Tend to Dissociate from Rhodium



showed the strong isomerization activity of the unmodified rhodium catalysts. Even with an excess of these phosphines, the nonligated catalyst dominated the reaction. The phosphines are characterized by cone angles (θ) of 165° and 188°, respectively.

Taking the fact into consideration that enhanced n-regioselectivity can be achieved by an excess of phosphine ligands in rhodium-catalyzed hydroformylation (see Scheme 15), Zhang et al. developed a special type of conformationally restricted biaryl tetraphosphines (Scheme 19). These ligands

Scheme 19. Tetraphosphines and their Graded Suitability for Isomerization−Hydroformylation

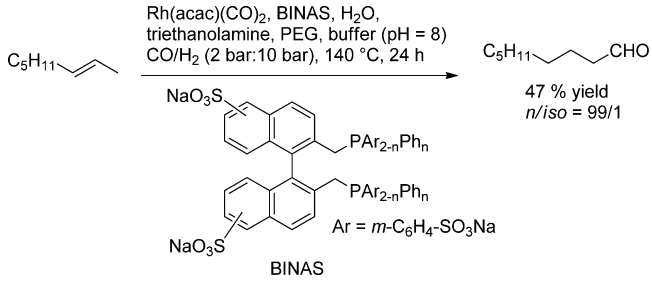


Ar = *p*-MeC$_6$H$_4$ < Ph ~ *m*-CF$_3$C$_6$H$_4$ ~ 3,5-(CF$_3$)$_2$C$_6$H$_3$ < 3,5-F$_2$C$_6$H$_3$ < *p*-CF$_3$C$_6$H$_4$

induce more than 95% selectivity in the formation of linear aldehydes, starting from 2-pentene, 2-hexene, or 2-octene.[45] It is assumed that these ligands own multichelating coordination properties. The n-regioselectivity increased with respect to the nature of Ar in the order found in Scheme 19, indicating the same electronic effect as found with IPHOS.

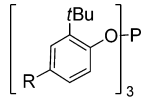
Using sulfonated NAPHOS-type ligands (so-called BINAS), Beller achieved n/iso ratios of up to 99:1 with 2-olefins, such as 2-octene, in an aqueous biphasic medium (Scheme 20).[98,106] Best TONs of 1460 and TOFs of 61 h^{-1} were noted at pH = 7−8.

Scheme 20. Isomerization−Hydroformylation in an Aqueous Two-Phase System



Organophosphites are weak σ-donors, but strong π-acceptors. This property facilitates the dissociation of CO from rhodium and the subsequent insertion into the Rh−acyl bond. As a result, the rate of the hydroformylation is enhanced.[107] Therefore, in rhodium-catalyzed isomerization−hydroformylation, the replacement of phosphines by phosphites may alter the ratio of product isomers. First, phosphites bearing sterically demanding 2-*tert*-butylaryl groups were claimed as ligands for hydroformylation by Shell[108] and UCC[109] (Scheme 21) and are still in use in industry.

Scheme 21. Monodentate Phosphite Ligands Used for Hydroformylation



R = H, Me, *t*Bu

Claver, Castillon, and Bayon found that regioisomeric aldehydes obtained in the hydroformylation of dihydrofurans strongly vary with the type of monodentate phosphorus ligand (Scheme 22).[110]

In general, 2*H*,5*H*-dihydrofuran, as a typical allyl ether, can easily isomerize under the effect of metal catalysts to form the corresponding 2*H*,3*H* isomer.[111] Both isomers can react with syngas. At moderate reaction conditions (5 bar, 80 °C) with the bulky monophosphite as a ligand, predominantly tetrahydrofuran-2-carbaldehyde was formed, whereas the use of PPh$_3$ forced the production of the 3-carbaldehyde. A similar feature was noted for dihydropyran. It is worth noting that only in the presence of syngas and rhodium catalyst did isomerization of

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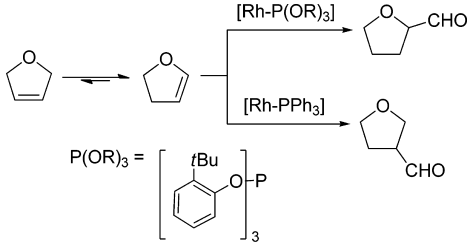
Scheme 22. Isomerization−Hydroformylation of Dihydrofurans in Dependence on Nature of the Phosphorus Ligand



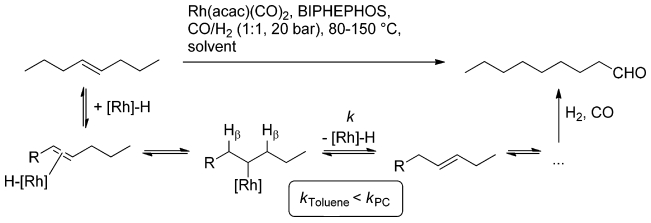
2*H*,5*H*-dihydrofuran took place. Moreover, with bulky ligands, the selectivity was almost independent of the P/Rh ratio.

As already discussed with phosphines, also with phosphites, relevant chelating ligands induce significantly higher selectivities in the isomerization−hydroformylation of internal olefins. First, ligands in this respect were synthesized by Bryant and coworkers at UCC, which gave excellent regioselectivities (n/iso = 19 for 2-hexene; n/iso = 17 for 2-octene).[112] Such biaryl-2,2′-diphosphites of the BIPHEPHOS-type became the prototype of all subsequently synthesized ligands (Scheme 23). Paciello and Röper concluded on the basis of a combined study using chemical modeling and kinetic investigations that among diphosphites of type **1**, the ligand **a** adopting a bite angle around β_n = 120° should be most n-regioselective in the isomerization−hydroformylation.[113]

Kragl and colleagues applied a Rh(BIPHEPHOS) catalyst to the hydroformylation of a mixture of (*E*/*Z*)-2-pentene.[114] At 160 °C and 30 bar syngas pressure, 99% conversion was observed. *n*-Hexanal was formed in a yield of 79% and a linearity of more than 99%. The activity of the catalyst corresponded to a TOF of 1975 h^{-1}. From these results, a superior efficiency of diphosphites in comparison to their diphosphine congeners can be concluded.

Behr's group investigated the tandem isomerization−hydroformylation of (*E*)-4-octene with a BIPHEPHOS-based catalyst in detail (Scheme 24).[115] In toluene as solvent at 125 °C and 20 bar syngas pressure, *n*-nonanal was formed at a yield of 88%. The yield of the terminal aldehyde was strongly dependent on the catalyst concentration.[116] Although the conversion rate of the olefin was rather constant, only at a rhodium concentration of 0.5 mol % was a high yield of *n*-nonanal noted. Under optimized conditions (10 bar, 125 °C, P/Rh = 6:1), a maximum TOF of 85 h^{-1} was achieved. The reaction in propylene carbonate (PC)[117] instead of toluene as solvent raised the n-regioselectivity to 95% (TOF = 34 h^{-1}).[115] This effect was rationalized by a higher mobility of the β-hydride

Scheme 24. Simplified Mechanism for the n-Regioselective Rhodium-Catalyzed Isomerization−Hydroformylation



atoms because of the polar PC in the relevant rhodium−alkyl complexes.[118]

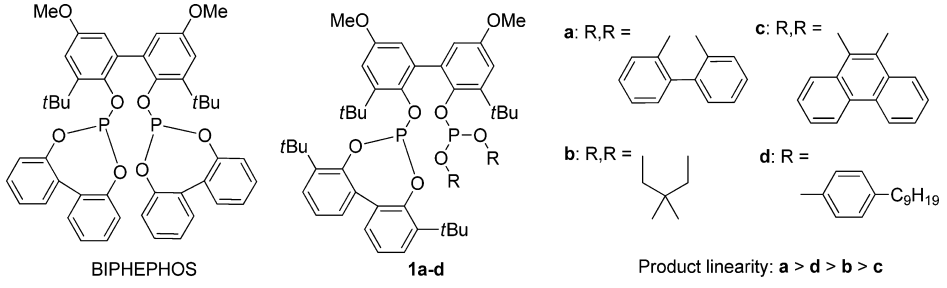
Beller's group investigated the influence of four bromo substituents in H_8-BINOL-derived diphosphites **1** (Scheme 25) on the hydroformylation of 2-pentene and 2-octene, respectively.[119] With some of these ligands, higher activities in comparison with BINAPHOS and similarly high n-regioselectivities were noted. As anticipated, the steric increase contributed by bromo atoms enhanced the n/iso ratio in comparison with the parent ligand (R═H).

During the last 15 years, we have developed several new ligands for the isomerization−hydroformylation of mixtures of isomeric *n*-octenes. Surprisingly, monophosphonite ligands **2** also induced moderate n-regioselectivity.[120] This result gives proof that instead of two ligating phosphorus groups, a hemilabile coordinating group in a monodentate P ligand can also contribute to the desired n-regiodiscriminating properties of the catalyst.[121] In comparison with BIPHEPHOS, benzpinacol-derived diphosphites, such as **3**, gave superior regioselectivities (99%) in the hydroformylation of 2-pentene.[31] Because of these outstanding properties, the ligand was used by Haumann and Wasserscheid in a supported ionic liquid phase reaction with a mixed C4-feed (Raffinate I).[7,122] At 120 °C and 20 bar syngas pressure, a space−time yield (STY) of 850 kg *n*-pentanal per cubic meter per hour was reached, which represents one of the highest STYs reported in the literature. Also under these conditions, the selectivity toward the formation of *n*-pentanal remained above 99%.

Up to 69% yield of linear nonanal was achieved in the rhodium-catalyzed hydroformylation of 2-pentene or isomeric *n*-octenes with electronically nonsymmetric acylphosphite−phosphites as ligands (Scheme 26).[123] Extremely high TOFs of 3000−7000 h^{-1} were calculated. Phosphites with methoxy substituents in the periphery of the ligand induced higher activity but lower regioselectivity than their *tert*-butyl counterparts.

These results could be further improved by application of anthracenetriol-based triphosphite ligands (Scheme 27).[124] In the reaction with 2-pentene, yields of >90% were noted, and *n*-

Scheme 23. Basic Structures of Large-Bite-Angle Diphosphites Suitable for Isomerization−Hydroformylation



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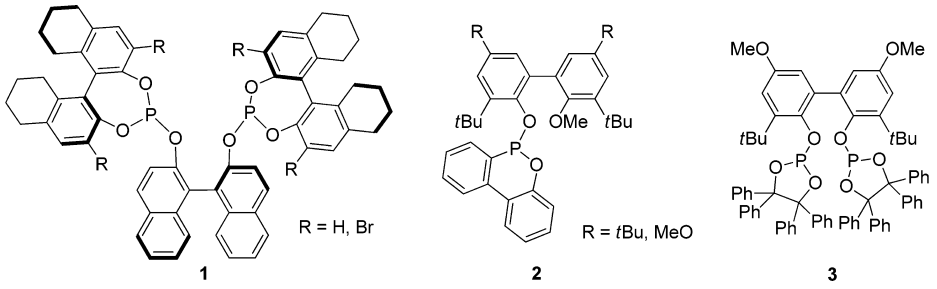
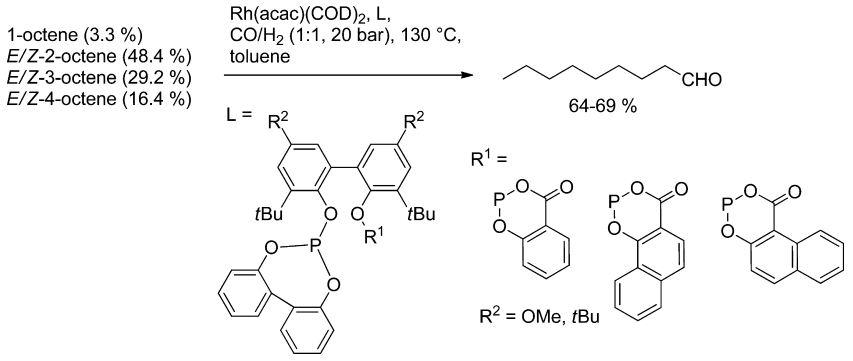
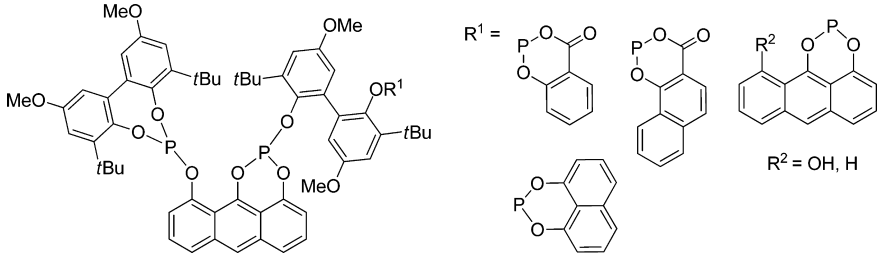
Scheme 25. Phosphites and Phosphonites Suitable for Isomerization−Hydroformylation



Scheme 26. Isomerization−Hydroformylation of *n*-Octene Mixtures



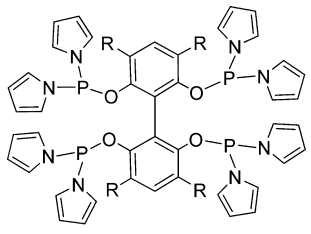
Scheme 27. Anthracenetriol-Based Triphosphite Ligands



hexanal was formed with 92−94% selectivity (CO/H_2 = 1:1, 2 MPa; 100−120 °C, 4 h; propylene carbonate or toluene). When a mixture of *n*-octenes was submitted, a linear selectivity in the product of 84−87% was achieved. Interestingly, with 2-butene as substrate, a slightly higher n-selectivity (90%) was observed in comparison with the use of 1-butene.

Pyrrole-based tetraphosphoramidites were suggested by Zhang and co-workers for the isomerization−hydroformylation of 2-octene and 2-hexene (Scheme 28).[125] The ligand/metal ratio had a dramatic effect on the regioselectivity. At a ratio of 1:1, low regioselectivities resulted. To achieve an n/iso ratio of ∼41:1, a minimum ligand/metal ratio of 2:1 had to be applied,

Scheme 28. Pyrrole-Based Tetraphosphoramidites



and the reaction had to be run at a temperature above 100 °C. By substitution in 3,3′,5,5′-positions (R) at the biphenyl unit, the selectivity could be further improved.[126] In the best case, a ratio of n/iso = 207 was reached. A clear conclusion about the contributions of steric or electronic effects could not be derived from these experiments.

Du Pont and DSM claimed the preparation and use of binaphthyl-derived diphosphites for the isomerization−hydroformylation of internal olefins (n/iso = 36 for 2-hexene) and methyl 3-pentenoate, respectively (Scheme 29).[127] In general, electron-withdrawing ester groups in the 3,3′-position of the diphosphite had a beneficial effect on the regioselectivity.

On a large-scale route to the noncanonical α-amino acid (*S*)-allysine, Cobley and Loyd employed the isomerization−hydroformylation of crotonaldehyde acetal as the central step (Scheme 30). With a Rh(BIPHEPHOS) catalyst at a substrate/catalyst ratio of 4000, glutaraldehyde monoethylene acetal was obtained with an n/iso selectivity of ∼15/1.[128]

A set of different reaction protocols allows a meaningful comparison of different phosphite ligands on the rhodium-catalyzed hydroformylation of methyl oleate (Scheme 31).

First, van Leeuwen and co-workers applied a homogeneous rhodium catalyst based on a sterically hindered monophosphite at 20 bar syngas pressure and 100 °C.[129] A fast isomerization of the *Z* into the *E* configurated fatty acid ester (methyl elaidate)

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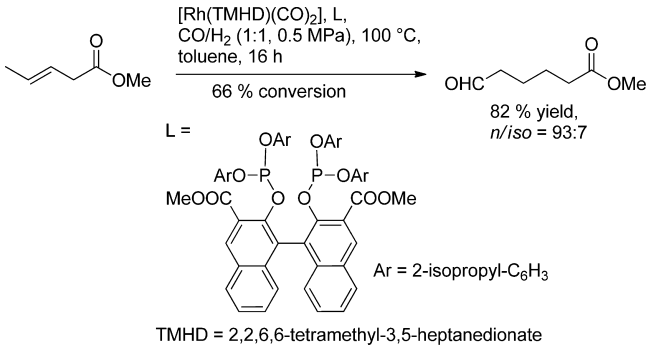
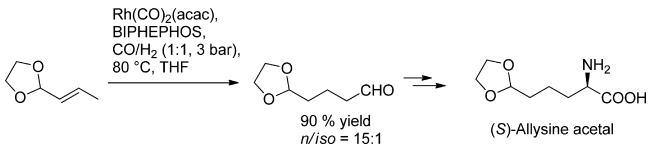
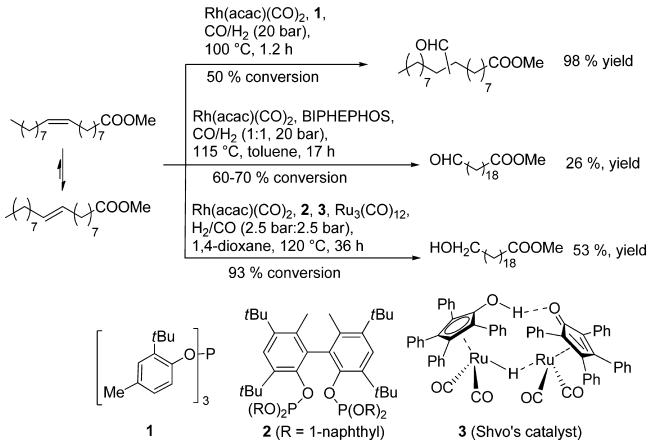
Scheme 29. Hydroformylation of Methyl 3-Pentenoate



Scheme 30. Isomerization−Hydroformylation to Glutaraldehyde Monoethylene Acetal



Scheme 31. Isomerization−Hydroformylation of Methyl Oleate with Different Rhodium Phosphite Catalysts



was noted. The latter reacted more slowly in the subsequent hydroformylation. Mainly C_9- and C_{10}-formyl stearates were obtained, which suggests that migration of the double bond is significantly slower than hydroformylation. Behr and co-workers reacted the same substrate with syngas in the presence of a Rh(BIPHEPHOS) catalyst at 20 bar syngas pressure to yield 18-formyl methyl stearate at a yield of 26%.[33] The regioselectivity was investigated as a function of the P/Rh ratio, syngas pressure, and temperature. Up to a P/Rh ratio of 10, the selectivity toward the formation of the terminal aldehyde increased, then it remained constant. Although the temperature dramatically influenced the conversion, the regioselectivity was not affected. At a syngas pressure of 10 bar, a maximum yield of MFS was noted. When ethyl linoleate was used as substrate, the linear aldehyde was formed at a yield of 34% at 5 bar syngas pressure. With the latter substrate, conjugation of the double bonds and a stronger hydrogenation activity of the rhodium catalyst was noted in comparison with methyl oleate.

In 2013, Nozaki's group reported a dual Rh/Ru catalyst based on a combination of a Rh(diphosphite), Shvo's catalyst and $Ru_3(CO)_{12}$ in the isomerization−hydroformylation−hydrogenation tandem reaction.[130] With methyl oleate, 53% yield of the terminal alcohol was observed. With unmodified internal olefins (2-decene, 2-tridecene, 4-octene), even higher regioselectivities in favor of the terminal alcohol could be achieved (n/iso up to 12/1). Proof was given that both rhodium and ruthenium complexes catalyze the isomerization−hydroformylation−hydrogenation in a cooperative manner.

Related to this work, Beller and Geissler advocated the application of bimetallic catalysts: one for the isomerization and the other for the hydroformylation.[131] Indeed, with a catalytic system comprising a rhodium complex based on a chelating phosphine−phosphite ligand and $Ru_3(CO)_{12}$ (0.1−0.5 mol %), almost a reversal of the regioselectivity in the reaction with (*E*)-2-butene in comparison to the monometallic rhodium catalyst (n/iso = 42:58; TOF = 700 h^{-1}) was achieved. This approach can be considered as "orthogonal tandem catalysis", since more than one noninterfering catalysts is present at the outset of the reaction.[9]

RUTHENIUM CATALYSTS

The use of ruthenium catalysts for hydroformylation can be traced back to the pioneering work of Wilkinson and colleagues in 1965.[132] A comparison of Rh and Ru catalysts in the hydroformylation of linear butenes[133] or 3,3,3-trifluoropropene allowed the conclusion that the latter are less active.[134] Moreover, in the hydroformylation of propene, an inferior regioselectivity was noted.[135] Apparently, ruthenium catalysts can show a pronounced isomerization activity, which is supported by heteroatoms in the substrate (e.g., allyl alcohols, allylamines).[136] Another typical side reaction is the hydrogenation of olefins or product aldehydes to give alkanes and alcohols, respectively.

Organic ligands tested were aromatic amines (2,2′-bipyridine, 2,2′-bipyrimidine, 1,10′-phenanthroline) and saturated cyclic amines and aliphatic amines (Et_3N) or simple amides, such as *N*,*N*-dimethylacetamide.[137] Kalck and co-workers investigated dinuclear ruthenium complexes modified with NEt_3 or PPh_3 for the hydroformylation.[138] Replacement of the latter by $P(OPh)_3$ diminished the rate of hydrogenation as well as the isomerization disposition. A similar effect was found by using an excess of phosphine.

Until now, almost exclusively terminal olefins have been screened in ruthenium-catalyzed hydroformylation.[3] One of the notable exceptions concerns the early investigations by Knifton.[139] He used ruthenium carbonyl "melt" catalysts, wherein the ruthenium carbonyls are dispersed in quaternary phosphonium salts with a low melting point. By addition of chelating N-donor ligands, such as 2,2′-bipyridyl, *n*-aldehydes could be produced.

Very recently, Beller's group discovered the beneficial effect of imidazole-substituted phosphine ligands in the framework of hydroformylation−reduction tandem reactions of terminal olefins.[140] It is noteworthy that the applied monophosphine ligand possesses a methoxy group, which probably coordinates in a hemilabile fashion on the metal. Surprisingly, with this catalytic system in hand, 2-octene as substrate was chemoselectively converted into *n*-nonanal when propylene carbonate (PC) was the solvent (Scheme 32).[141] In contrast to the reaction with 1-alkenes, hydroformylation started at only 130 °C. Under these relatively severe conditions, hydrogenation of the formed olefin took place. By increasing the catalyst loading from 0.033 mol % to 0.1 mol %, this side reaction was suppressed, and the reaction could be run even at 100 °C. In

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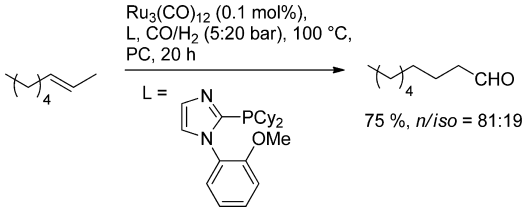
Scheme 32. Hydroformylation of 2-Octene in the Presence of a Ruthenium Catalyst



addition, an excess of hydrogen applied in the syngas mixture did not promote reduction of the aldehyde.

PLATINUM CATALYSTS

Usually, platinum catalysts stimulate extensive isomerization of nonfunctionalized olefins. Nevertheless, they have been screened for asymmetric hydroformylation, in which migration of the double bond to a (achiral) terminus is not desired. Frequently, this problem has been overcome by use of styrenes as model substrates, which direct the hydroformylation to the position next to the aryl ring.[142] Whether the olefin insertion or the subsequent carbonylation is the regiochemistry determining step is still under discussion.[143,144]

In the early 1970s Clark and Kurosawa intensively investigated the mechanism of the stoichiometric and catalytic isomerization of terminal and internal olefins (1-butene, allyl ethers) with phosphine-modified platinum hydrido complexes of the type *trans*-[$HPt(PR_3)_2$(acetone)]X and *trans*-[$HPt(ClO_4)(PPh_3)_2$].[145] Later on, Toniolo et al. showed that the isomerization rate is strongly dependent on the temperature.[146] In addition, hydroxyl groups being a constituent of allyl alcohols may direct the isomerization.[145]

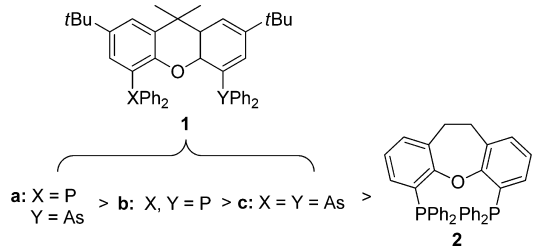
Some hydroformylation studies were carried out with the aim to generate *n*-aldehydes from terminal as well as internal olefins.[147] A group at Shell investigated the reaction of long-chain internal olefins with a catalyst of the type [$PtCl(CO)(PR_3)_2$]$ClO_4/SnCl_2$.[148] The regioselectivity in favor of the linear aldehyde increased in the following order, thus finally characterizing PPh_3 as a superior ligand:

$$PnBu_3 < < P(OPh)_3 < P(o\text{-}MeOC_6H_4)_3 \approx P(m\text{-}MeC_6H_4)_3 < PPh_3$$

The n/iso ratio with the PPh_3-based catalyst increased continuously, going from 80 to 140 °C. At 180 °C, the conversion dropped, probably because of a decomposition of the catalyst. Although conversion and chemoselectivity increased with increasing syngas pressure, the regioselectivity eroded. The n/iso ratio was only slightly affected by the partial pressures of CO and H_2.[149] Monodentate arsines as ligands were found to be less efficient.[150]

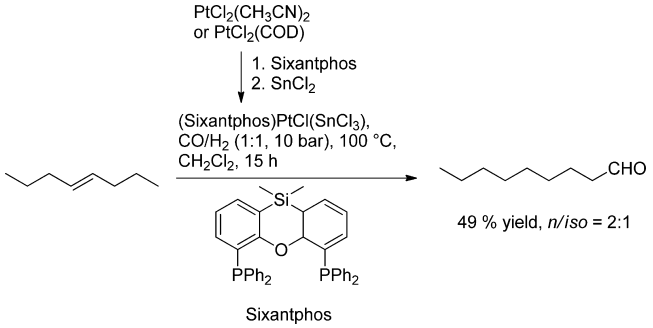
Van Leeuwen tested the concept of a large bite angle also in the Pt/Sn hydroformylation of 1-octene (Scheme 33).[151] Excellent n-regioselectivities (92–96%) using Xantphos-type ligands were noted. Geometries similar to those of catalytic intermediates found with rhodium congeners were concluded. Surprisingly, the mixed phosphine–arsine ligand **1a** (β_n = 111°)[152] induced the highest selectivity. In contrast, ligand **2**, which adopts a narrow bite angle of β_n = 102°,[152] induced a 40-fold higher hydroformylation rate, but its use was accompanied by a significantly higher isomerization tendency.

Scheme 33. Suitability of Phosphines and Arsines for Platinum/Tin Catalyzed n-Regioselective Hydroformylation



Vogt and co-workers studied the isomerization–hydroformylation of 4-octene with a catalyst generated by the reaction of Sixantphos with $PtCl_2$ and $SnCl_2$ (Scheme 34).[153]

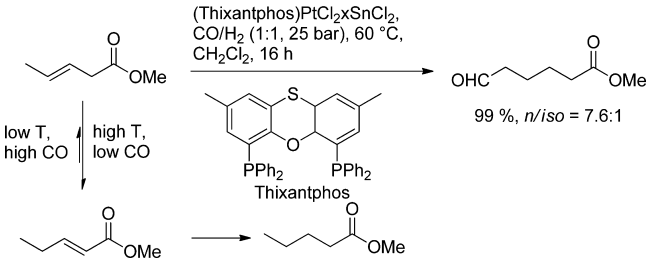
Scheme 34. Pt/Sn Catalyzed Isomerization–Hydroformylation of 4-Octene



For the diphosphine, a bite angle of ∼106° was calculated.[154] The isomerization activity of the catalyst and the n/iso ratio increased with temperature. Long reaction times and temperatures above 100 °C led preferentially to hydrogenation of the olefin.

The same research group investigated the Pt/Sn-catalyzed isomerization–hydroformylation of methyl 3-pentenoate (Scheme 35).[154] The product methyl 5-formylpentanoate can

Scheme 35. Pt/Sn Catalyzed Isomerization–Hydroformylation of Methyl 3-Pentenoate



be converted to adipinic acid, an important starting material for the synthesis of nylon 6.6. At higher temperature and low CO pressure, the isomerization of 3-pentenoate into the thermodynamically more stable 2-pentenoate became a serious issue. The latter is preferentially hydrogenated under these conditions. In contrast, at lower temperature, a catalyst based on Thixantphos (β_n = 107°)[155] gave the desired aldehyde exclusively. Later on, van Leeuwen confirmed these results using a related Xantphos ligand.[152] Replacement of one or both PPh_2 groups with $AsPh_2$ reduced the undesired hydrogenation activity but simultaneously lowered the yield of the hydro-

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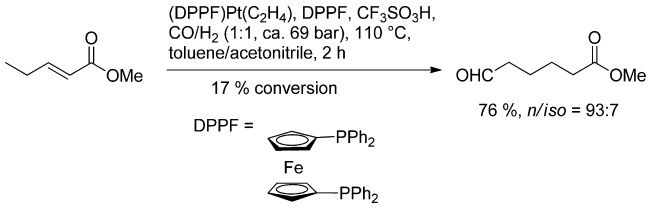
formylation reaction. Wasserscheid and Waffenschmidt noted that by running the reaction in ionic liquids, such as 1-butyl-3-methylimidazolium chloride ([BMIM]Cl) or 1-butyl-4-methylpyridinium chloride ([4-MBP]Cl) instead of CH_2Cl_2, the activity of the Pt/Sn catalyst can be enhanced.[156]

DuPont claimed the use of a bis(diphenylphosphino)ferrocene-based tin-free Pt catalyst for the isomerization−hydroformylation of the same substrate and at 35% conversion obtained >86% of methyl 5-formyl pentanoate with a linearity of 93%.[157] Instead of the methyl ester, the free acid could also be successfully employed as the substrate. In the case of less regioselective hydroformylation, 5-formylvaleric acid can be advantageously separated from the other isomers by crystallization in methyl *tert*-butyl ether (MTBE).[158]

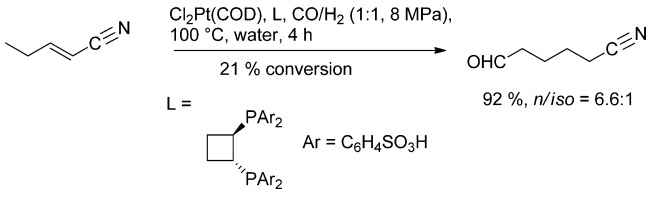
Under the same catalytic conditions, even the isomeric substrate methyl 2-pentenoate reacted to yield the desired *n*-aldehyde with 76% chemoselectivity (Scheme 36).[157]

Scheme 36. Sn-Free Pt Catalyzed Hydroformylation of Methyl 3-Pentenoate



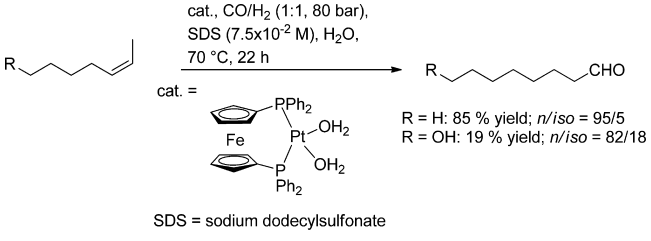
Platinum-catalyzed isomerization−hydroformylation of (*E*)-3-pentenenitrile was realized in an aqueous two-phase system with a tetrasulfonated diphosphine as ligand, which at low conversion gave mainly the linear aldehyde (Scheme 37).[158]

Scheme 37. Sn-Free Platinum-Catalyzed Hydroformylation of (*E*)-3-Pentenenitrile



Scarso and Strukul discovered that internal olefins such as 2-heptene can be hydroformylated with an n/iso ratio of 95/5 employing a water-soluble, tin-free Pt(II) catalyst in the presence of micelles (Scheme 38).[159] Incorporation of a hydroxyl group at the remote terminal position (R═OH) dramatically diminished the yield of the reaction and led to an erosion of the n-regioselectivity. This result was attributed to the lower solubility of the substrate in the apolar core of the micelle.

Scheme 38. Sn-Free Platinum-Catalyzed Isomerization−Hydroformylation of 2-Heptene

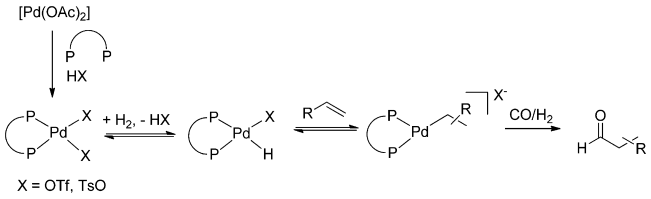


PALLADIUM CATALYSTS

Until now, palladium complexes have not played a significant role in the hydroformylation of olefins,[3] although recently, their value in the hydroformylation of alkynes has been proven.[160] However, because of their widespread use in the related hydrocarboxylation, hydroesterification, and olefin copolymerization with CO,[161] occasionally their utility for hydroformylation has been tested.[162] Palladium complexes are able to assist in the *Z*/*E*-isomerization and migration of a variety of olefins. Heteroatoms in the olefin and trialkyl- or dialkylphosphines have been used as ligands for palladium support isomerization.[163]

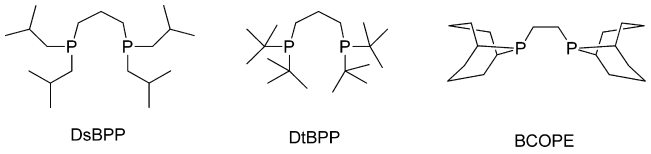
The mechanism of the hydroformylation has been intensively investigated by Drent and co-workers, who analyzed the competition between alternative reactions (hydroacylation, copolymerization) once the Pd−acyl complex has been formed from a palladium hydride species (Scheme 39).[164] Frequently, aldehydes are immediately reduced to the corresponding alcohols under hydroformylation conditions.

Scheme 39. Crucial Steps of the Palladium-Catalyzed Hydroformylation



In addition to the nature of the anion (X), phosphine ligands play a pivotal role. Bulky diphosphines such as (DsBPP), 1,3-bis[(di-*tert*-butyl)phosphine]propane (DtBPP), and bis(9-phosphabicyclo[3.3.1]nonyl)ethane (BCOPE), can be used to adjust the steric environment around the Pd center (Scheme 40).[165] Sterically demanding substituents on the phosphorus increase the formation of the linear aldehydes/alcohols.

Scheme 40. Diphosphine Ligands for Palladium-Catalyzed Hydroformylation



Halide anions affect the rate of the hydroformylation of internal olefins as well as the regioselecting properties of the catalyst.[165] The rate of hydroformylation of thermally equilibrated internal higher alkenes increased by a factor of about 6−7 with addition of substoichiometric amounts (with respect to palladium) of Cl^- or Br^- and about a factor of 3−4 with I^-.[166] When a thermally equilibrated mixture of internal C_8−C_{10} olefins was subjected to isomerization−hydroformylation, a reversed effect on the regioselectivity was observed.[165e] Thus, the formation of the linear aldehyde increased in the order: iodide > bromide > chloride.

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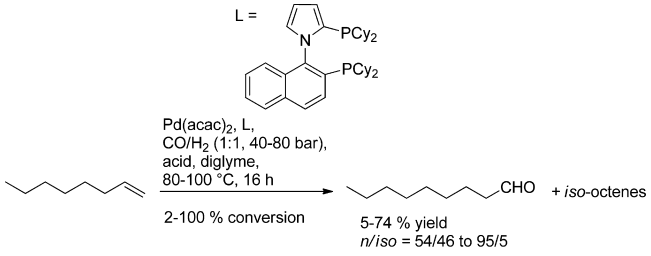
Palladium-mediated hydroformylation of several terminal and internal olefins was investigated by the Beller group, too (Scheme 41).[167] By stirring 1-octene at room temperature in the presence of the catalyst without any hydrogen pressure, fast isomerization took place. Within 1 h, 1-octene was almost completely equilibrated to give a mixture of internal olefins. Hydroformylation trials at 40 or 80 bar syngas pressure and at 80 or 100 °C revealed the strong influence of these parameters on the success of the reaction.

Scheme 41. Palladium-Catalyzed Hydroformylation of 1-Octene under Different Conditions



a) *p*-TsOH; T = 80 °C, p = 40 bar: 98 % conversion; 24 % aldehydes with *n*/*iso* = 70/30; 68 % *iso*-octenes.
b) *p*-TsOH; T = 100 °C, p = 80 bar: 99 % conversion; 72 % aldehydes with *n*/*iso* = 81/19; 23 % *iso*-octenes.

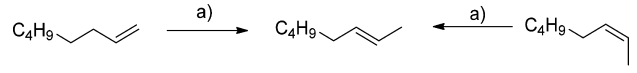
Moreover, the acid (e.g., *p*-TsOH, HBF_4, HCl, $ZnCl_2$, MsOH) also strongly affected the regioselectivity. For example, in the presence of 0.075 mol % of *p*-TsOH, the n/iso ratio was 95:5, whereas using 10 mol % of *p*-TsOH, *n*-nonanal and 2-methyloctanal were formed in a ratio of 54:46. In general, large differences were concluded in comparison with rhodium catalysts.

IRON CATALYSTS

Iron complexes display a high ability for the isomerization of functionalized (e.g allyl alcohols) and nonfunctionalized olefins.[23,168] In 1966, Frankel noted the isomerization activity of simple iron carbonyls.[169] In the presence of $Fe(CO)_5$ by heating to 180−185 °C, polyunsaturated fatty acid esters, such as methyl linoleate and methyl linolenate, gave the corresponding conjugated polyenes mainly in the *E* configuration. Later on, Wells and co-workers showed that with $Fe_3(CO)_{12}$, 1-pentene is already isomerized to 2-pentene at much lower temperatures (50 °C).[25] In addition, photoexcitation (wavelength 355 nm) stimulates isomerization assisted by iron carbonyls.[170] Under these conditions, phosphorus ligands, such as PPh_3, $P(OMe)_3$, or $P(O\text{-}o\text{-tolyl})_3$, shifted the isomerization equilibria of 1-pentene toward 2-pentene. The observed ratio of (*E*/*Z*)-2-pentene was dependent on only the steric bulk of the phosphine. More sterically demanding ligands led to an enrichment of the less thermodynamically stable alkene and gave smaller ratios of *E*/*Z*.

Beller and co-workers broadened these investigations to several other terminal functionalized and nonfunctionalized olefins as substrate (allyl alcohols, homoallyl alcohols, allylamines, homoallylamines, vinyl cyclohexane, 3-arylprop-1-enes).[171] For example, in a basic medium, $Fe_3(CO)_{12}$ converted 1-octene cleanly in 2-octene (Scheme 42). Moreover, (*Z*)-2-octene was converted into the corresponding *E* isomer. Temperatures of 80−100 °C were required to achieve nearly quantitative yields.

Scheme 42. Isomerization of 1-Octene in the Presence of an Iron Catalyst

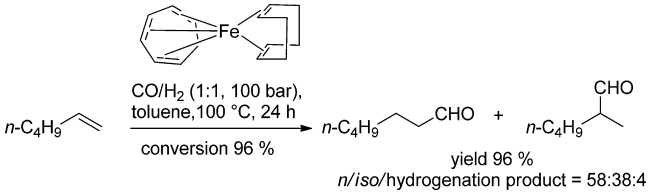


a) = $Fe_3(CO)_{12}$, KOH, H_2O, diglyme, 80 °C, 1 h

In contrast to the good isomerization activities of homogeneous iron carbonyls, there are only a few attempts described in the literature to use them in hydroformylation.[3] Iron pentacarbonyl $Fe(CO)_5$ itself is a very poor hydroformylation catalyst, as first shown in reaction with ethylene[172] and propylene.[173] Addition of PPh_3 as the ligand to the hydroformylation of 1-pentene improved the activity, but no marked change in regioselectivity was noted.[174]

Much higher yields were reported by Pertici and co-workers using syngas and an iron precatalyst stabilized by the polyolefins 1,3,5-cycloheptadiene and 1,5-cyclooctadiene (Scheme 43).[175] Aldehydes were formed almost quantitatively, but with only moderate n/iso selectivities. Other isomers were not detected.

Scheme 43. Rare Example of the Hydroformylation with an Iron Catalyst



Mixtures of homogeneous rhodium and iron catalysts were tested in the hydroformylation of 1-hexene by Trzeciak and Ziółkowski.[176] In the absence of a rhodium complex, $Fe(CO)_5$ did not show any catalytic activity at 80 °C and 10 atm of syngas pressure. Addition of $[Rh(acac)(CO)_2]$ led to the formation of 2-hexene and eventually 3-hexene, but no aldehyde was formed. Only when $[Rh(acac)(CO)(PPh_3)]$ was added did hydroformylation commence. The bimetallic catalyst benefited from the presence of additional PPh_3. At a ratio of P/Rh = 3, a rate acceleration of ∼2 times was noted, and finally, 83% yield of aldehyde could be produced. No change in the n/iso ratio was noted because of these modifications.

TANDEM ISOMERIZATION−HYDROFORMYLATION REACTIONS WITH CONSECUTIVE STEPS

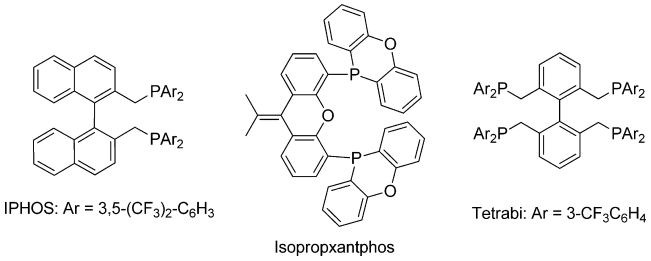
A particular challenge constitutes isomerization−hydroformylation tandem reactions terminating with further catalytic steps. A typical example is the hydrogenation of formed aldehydes to give alcohols (see, for example, the last reaction in Scheme 31). Another approach represents hydroaminomethylation, consisting of isomerization, hydroformylation, reaction of the intermediate aldehyde with amine, and final hydrogenation of the imine or enamine.[11,177,178] Examples are rare because for better controllability, most investigations start with a defined terminal olefin. This reduces the number of possible isomeric products.

In 2002, Beller and co-workers discovered that by application of a rhodium catalyst based on a bidentate IPHOS ligand

dx.doi.org/10.1021/cs500273d | ACS Catal. 2014, 4, 1706−1724

(Scheme 44), several internal olefins (2-butene, 2-pentene, 3-pentene, 2-hexene, 3-hexene) react with syngas and primary or

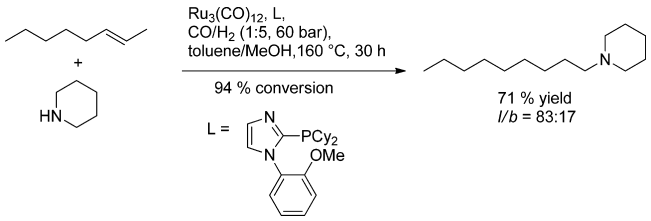
Scheme 44. Ligands for Highly n-Regioselective Rhodium-Catalyzed Hydroaminomethylation of Internal Olefins



secondary amines in a one-pot reaction to give tertiary amines with a linear selectivity between 68 and 90%.[179] The regioselectivity was only slightly dependent on the temperature and the catalyst concentration. Later studies in collaboration with van Leeuwen's group showed that also with xanthene-based ligands high yield and regiodiscrimination can be achieved.[180] Superior linearity (n/iso = 24:1 with 2-pentene and piperidine; n/iso = 16:1 with 2-octene and morpholine) in the formed products was noted, with Isopropxantphos characterized by a natural bite angle of 114°. In 2012, Zhang and co-workers gave proof that tetraphosphine ligands (meanwhile called Tetrabi) can also be advantageously used for this reaction.[181] The highest n-regioselectivity (n/iso = 96:1, 2-pentene and piperidine) and amine selectivity (99%) were observed with tetraphosphines bearing electron-withdrawing groups.

Quite recently, the rhodium-based protocols were extended to a ruthenium catalyst modified with a monodentate 2-phosphino-substituted imidazole ligand on the hydroaminomethylation of 2-octene (Scheme 45).[182]

Scheme 45. Ruthenium-Catalyzed Hydroaminomethylation of 2-Octene with Piperidine



CONCLUSIONS

Although more than 75 years old, the question of highly regioselective hydroformylation of olefins continues to be an important subject for homogeneous catalysis. Because of the broad availability of feeds containing mixtures of double bond isomers or even predominantly internal olefins, the isomerization–hydroformylation tandem reaction to give terminal aldehydes is of utmost interest not only on a small laboratory scale but also for a number of industrial fine and bulk chemical processes. Major advances have been made in the rhodium-catalyzed transformation based on chelating phosphorus ligands with carefully tuned bite angles and special electronic properties, but with these catalytic systems, a more detailed knowledge of how the organic ligands manage the competition between isomerization and hydroformylation would be helpful. In particular, the geometric structure of preferred catalyst–substrate complexes, together with kinetic data of both competing reactions, could contribute to a better fine-tuning of the tandem reaction.

In contrast to cobalt or rhodium, other metals, which display either isomerization or hydroformylation activity and which might be less expensive, require further research. In particular, the application of iridium catalysts for this purpose warrants attention.[3] First reports give cause for some hope.[183] A further challenging field will be the isomerization–hydroformylation of α-olefins with the aim of achieving high regio- or even stereodifferentiation in the formation of internal chiral aldehydes.[184]

AUTHOR INFORMATION

Corresponding Author

*E-mail: armin.boerner@catalysis.de.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Prof. Dr. M. Beller, Dr. Ch. Kubis, Dr. R. Jackstell, and Dr. D. Selent for helpful discussions.

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