Tandem Reaction Sequences under Hydroformylation Conditions: New Synthetic Applications of Transition Metal Catalysis

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Received April 22, 1999 (Revised Manuscript Received June 24, 1999)

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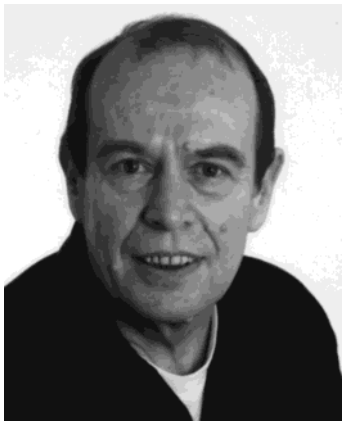
I. Introduction

Hydroformylation of alkenes is established as an important industrial tool for the production of aldehydes and products derived therefrom. Discovered in 1938 by Roelen, this process starts from petrochemical (alkene) and various other basic feedstocks (carbon monoxide, hydrogen). As a straightforward addition reaction of inexpensive starting materials, it is a clean and economical method. Numerous reviews on synthetical and industrial use,[1−9] mechanistic aspects,[5,10,11] and asymmetric/enantioselective versions[12−18] of hydroformylation are available. Hydroformylation is catalyzed by homogeneous catalysts including heterogenized[19−21] or biphasic alternatives.[22]

Aldehydes produced via hydroformylation usually are not the final products. Due to the versatile chemistry of the aldehyde group[23] they are further converted via reduction, oxidation, or other reactions to give alcohols, amines, carboxylic acid derivatives, aldol condensation products, and many others. Following a general trend in organic chemistry,[24−27] hydroformylation can also be integrated in tandem or domino reaction sequences. Thus, reduction, nucleophilic addition, or aldol condensation can be achieved directly under the reaction conditions of hydroformylation (see below). This, however, is not trivial in all cases, since additional reagents, products, or variations of reaction conditions optimized for hydroformylation may suppress or hinder the initial hydroformylation step. Thus alcohol formation via reduction of the oxo aldehyde occurs under forcing conditions and may lead to acetals with the nonreduced aldehyde present. Similarly, many other reactions of the metal acyl intermediates or the final aldehydes may occur under hydroformylation conditions as collected in Scheme 1. Indeed, some of these reactions are either undesired side reactions or are optimized as the major reaction pathway.[1−3]

In this review examples of two or more step conversions of unsaturated compounds under hydroformylation condition involving initial hydrocarbonylation and additional conversions of intermediates

10.1021/cr970413r CCC: $35.00
Published on Web 10/09/1999



Peter Eilbracht, born in 1943 in Mannheim, Germany, studied chemistry in Darmstadt with his doctoral thesis under the supervision of Klaus Hafner. After a postdoctoral year at the IBM Research Laboratories in San Jose, CA, he started his own research projects at the Technische Hochschule Darmstadt (Habilitation 1978) where he was assigned C2-Professor in 1980. During this time he spent a year as Visiting Scientist at the Max-Planck-Institut in Mülheim, Germany (1978/1979). In 1983 he was assigned C3-Professor at the University of Duisburg, and since 1993 he has held a chair of Organic Chemistry at the University of Dortmund, Dortmund, Germany. His research interests cover the area of organometallics, metal-mediated CC bond cleavage, and transition metal catalysis, especially carbonylation reactions and stereoselective organic synthesis.

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Beate E. Kitsos-Rzychon, born in 1969 in Kattowitz, Poland, studied chemistry in Dortmund and finished her doctoral thesis on tandem hydroformylation of unsaturated alcohols in 1998 under the supervision of P. Eilbracht. She recently joined the Byk Gulden Lomberg GmbH at Konstanz, Germany.

or the aldehyde product are compiled and cover the literature up to the end of 1998.

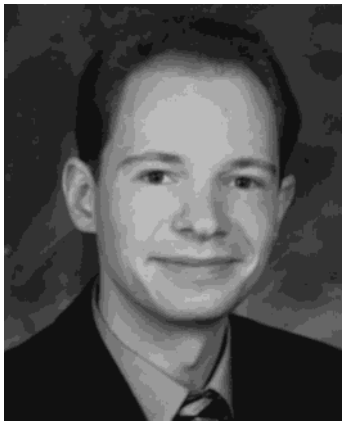
The material described is ordered according to the type of the additional bond-forming reaction, e.g. C−H (reduction), C−O (acetals, enol ethers), C−N (aminals, enamines), C−C (coupling, aldol addition, olefin insertion with ketone formation), or other types of conversion. The subject of this review has hitherto not been described in depth but is part of several more general reviews.[3,8,28]

II. Hydroformylation/Reduction Sequences

In normal hydroformylation processes reduction of the aldehyde products to alcohols is one of the common parallel and consecutive reactions lowering yield or selectivity and leading to undesired side products. In the case of alcohol formation via reduction of oxo aldehydes this not only lowers the aldehyde yield but also may lead to consecutive reaction to form formic acid esters (with CO), acetals (with oxo aldeydes), and "heavy ends" (via aldol condensation, acetalization, trimerization and others).

Reduction of aldehydes to alcohols, however, under controlled conditions can also be used as a method

Christian L. Kranemann, born in 1970 in Werne, Germany, studied chemistry in Dortmund and at the University College, London. He just finished his doctoral thesis under the supervision of P. Eilbracht. Major topics of his research are hydroaminomethylation and macroheterocyclic ring synthesis.



Thorsten Rische, born in 1971 in Unna, Germany, studied chemistry in Dortmund and finished a doctoral thesis on the hydroaminomethylation of olefins in 1999 under the supervision of P. Eilbracht. He is now working at the Bayer AG, Leverkusen, Germany, as a research scientist.

Rafael Roggenbuck, born in 1972 in Gelsenkirchen, Germany, studied chemistry in Dortmund and presently works on his doctoral thesis under the supervision of P. Eilbracht. His research concentrates on heterocyclic ring synthesis via tandem hydroformylation.

for direct alcohol synthesis. Considerable efforts have been made to optimize this process.[1−5,8] Thus, alcohols are the major products, if hydroformylation is carried out with cobalt or rhodium catalysts under forcing conditions with higher hydrogen pressure in the presence of phosphines. Furthermore addition of amines, N-donors, or alcohols promotes direct alcohol

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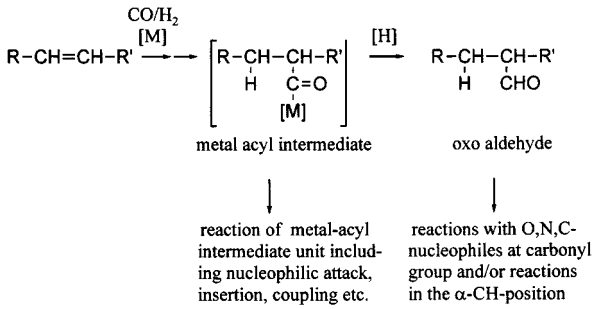
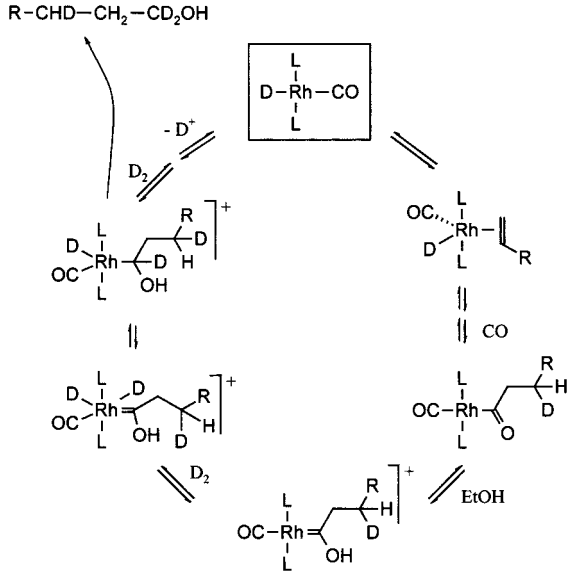
Scheme 1



Scheme 2

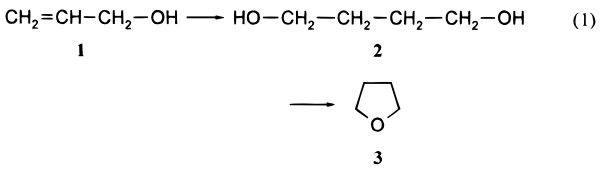


formation.[29] More recently methodical and mechanistic investigations on rhodium-catalyzed hydroformylation/reduction of 1-hexene to 1-heptanol with $[RhH(PEt_3)_3]$ or $[RhH(CO)(PEt_3)_2]$ in ethanol showed that aldehydes must not necessarily be the intermediates in direct alcohol formation. An alternative mechanism via protonation of the metal acyl intermediate and hydrogen transfer to a hydroxycarbene intermediate was proposed in accordance with labeling experiments (Scheme 2).[30−32]

Hydroformylation/reduction sequences are also achieved with zwitterionic $[Rh(cod)]BPh_4$ in the pres-

ence of $NaBH_4$ as reducing agent.[33] For industrial processes the direct alcohol formation would be advantageous in the production of lower or higher alcohols as solvents, plasticizers, or detergent alcohols.[31,32,34,35]

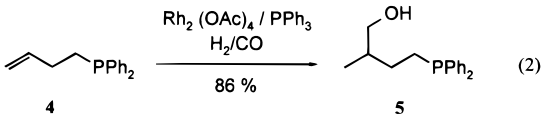
Up to now, however, all these processes are still performed in stepwise procedures since no commercial process allowing this conversion under mild conditions has been developed. Hydroformylation/reduction of functionalized alkenes leads to functionalized alcohols.[36] A useful application of this type is the direct conversion of allylic alcohol (**1**) to butanediol (**2**) or tetrahydrofuran (**3**).[36]



1 2 3 (1)

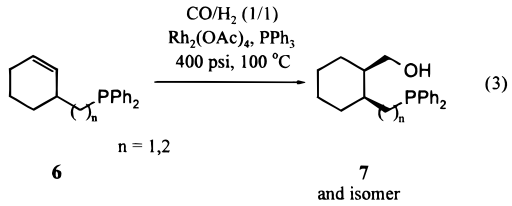
Similarly other alkenes and unsaturated alcohols are directly converted to alcohols and diols under hydroformylation conditions if using zeolite encapsulated rhodium(I) species[37,38] or other rhodium catalysts.[39]

Conversion of unsaturated phosphine **4** directly leads to phosphino alcohol **5** with high yields and isoregioselectivity (eq 2).[40−42]



4 5 (2)

Due to intramolecular chelation, the amount of reduction vs aldehyde formation depends on the chain length between the alkene and the phosphine unit (n = 1, 2, alcohol; n = 3, mixture; n = 4, aldehyde). In similar reactions of cyclic alkenes bearing phosphine groups additional stereocontrol is observed.[41] A typical example is described in eq 3.



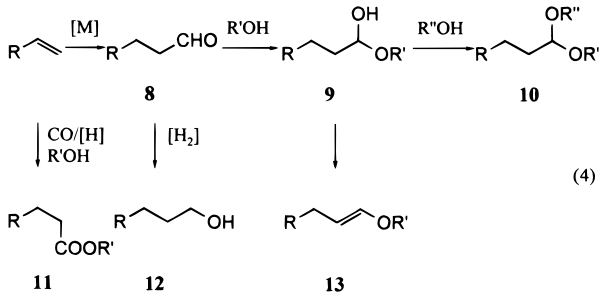
6 7 and isomer (3)

In a detailed study isolation and characterization of analogues of the chelating intermediates are described.[42]

Various other combinations of hydroformylation/reduction sequences are feasible. Thus the sequences might be combined with alcohol homologation and introduction of several carbon monoxide units resembling Fischer−Tropsch synthesis.

III. Tandem Hydroformylations in the Presence of O-Nucleophiles

Acetal formation is a typical addition reaction of aldehydes and frequently used in organic synthesis. Acetal formation under hydroformylation conditions can be expected if either alcohols (R′OH) are added or alcohols **12** are formed from the olefin via hydroformylation and reduction of the oxo aldehyde **8.** Therefore, the hydroformylation process can be combined with acetalization in a single reaction sequence to form hemiacetals **9,** acetals **10,** or enol ethers **13** (eq 4).



8 9 10 (4)

11 12 13

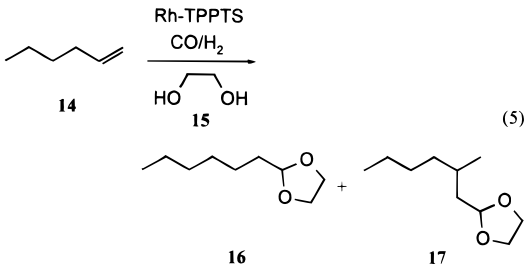
Acetal formation under hydroformylation conditions may be used to modify the aldehyde unit for further synthetic purposes or in order to protect the sensitive aldehyde group in the stereogenic α-position, respectively, e.g. in asymmetric hydroformylation.

If, however, the hydroformylation reaction is performed in the presence of alcohols or in alcohol solvents, hemiacetals, acetals, or enol ethers might not be observed as the major products. Instead in the presence of alcohols as hydrogen source the conversion can lead to reduction of the oxo aldehydes[1−8,30−32] or hydroesterification to form saturated esters of type **11** (eq 4).[43] The latter reaction, also known as hydrocarboxylation, proceeds in an alternative pathway not involving hydrogenolysis to aldehydes in the last step.[1]

A. Intermolecular Acetal Formation

a. In the Presence of Alcohols

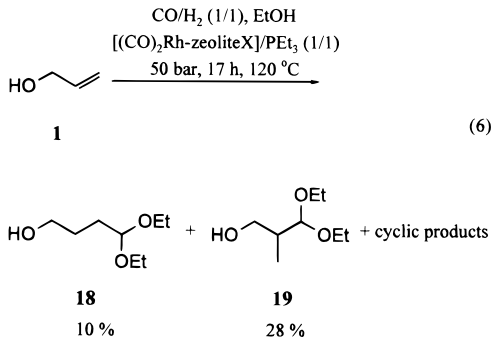
Various examples of direct acetal formation under hydroformylation conditions in the presence of alcohols are reported.[1−8] Thus hydroformylation of 1-hexene (**14**) in biphasic catalysis using ethylene glycol (**15**) as cosolvent directly leads to the corresponding acetals **16** and **17** of the oxo aldehydes[44] (eq 5).



14 15 (5)

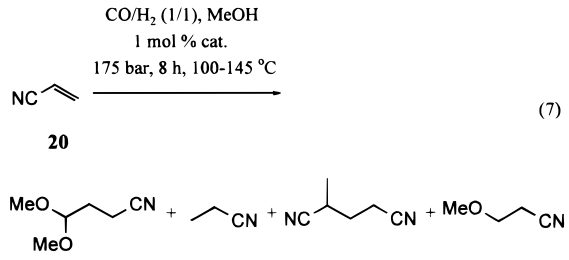
16 17

Under the conditions of hydrocarbonylation allylic and homoallylic alcohols can undergo acetalization with zeolite-encapsulated rhodium catalysts.[37] With these catalysts both intermolecular and intramolecular acetalization is observed. The highest yields of intermolecular acetals **18** and **19** are obtained with ethanol if zeolite X is used (eq 6). Obviously acetal formation in enhanced in the presence of acid or Lewis acid catalysts. In all cases, however, cyclization products prevail (see below).



Similar hydroformylations with subsequent acetal formation of the oxo aldehyde with methanol as solvent are achieved with the binuclear complex $[Rh_2(\mu\text{-}S(CH_2)_2NMe_2)_2(cod)]$, which is anchored to a sulfonic exchange resin through protonation of the residual amine groups. With this catalytic system styrene yields 1,1-dimethoxy-2-phenylpropane in 85% selectivity[45] (see also eq 8).

The conversion of cyano olefins to cyano aldehydes is of great interest because of their potential use as precursors for amino acids. If cobalt-catalyzed hydroformylation is performed in alcohol solvents, cyano acetals (e.g. **21**) are isolated.[36,46] Especially the reaction of acrylonitrile **20** in methanol has been examined. Here, however, with use of highly temperature sensitive $Co_2(CO)_8$ side products are generated by hydrogenation (**22**), dimerization (**23**), and Michael addition (**24**) of the alcohol. Addition of ligands produces systems that are more selective and temperature stable, entry 2 vs entry 4 (eq 7).[47] By

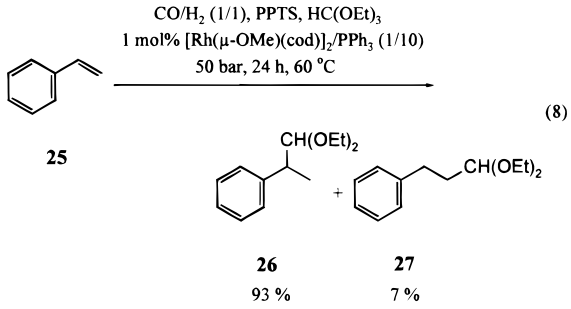


entry	catalyst	21	22	23	24
1	$Co_2(CO)_8$, 100 °C	90 %	4 %	2 %	-
2	$Co_2(CO)_8$, 145 °C	42 %	17 %	15 %	-
3	$Co_2(CO)_8$ + 2 $HN(CH_2CN)_2$, 100 °C	93 %	3 %	2 %	-
4	$Co_2(CO)_8$ + 2 $HN(CH_2CN)_2$ 145 °C	84 %	6 %	1 %	-

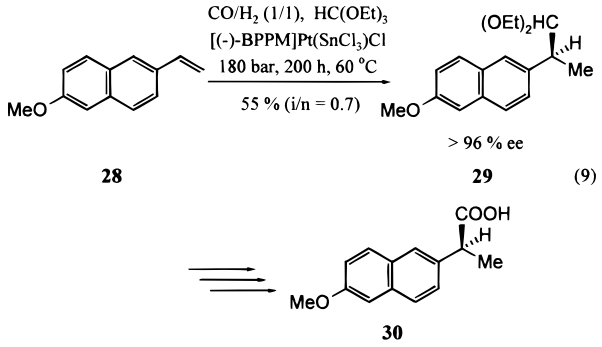
modification of the cobalt carbonyl catalysts with ligands such as $HN(CH_2CN)_2$, $H_2C(CH_2)_3NMe$, $Me_2N(CH_2)_2NHMe$, PPh_3, and PCy_3, up to quantitative yields of the acetals are obtained.[36,46,47]

b. In the Presence of Ortho Esters or Other Reagents

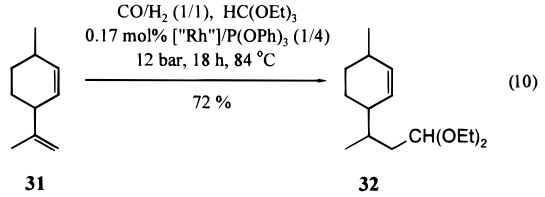
Selective formation of acetals from alkenes under hydroformylation conditions can also be achieved with triethyl orthoformate or 2,2-dimethoxypropane (DMP) instead of alcohols as the reagent. Various rhodium catalyst precursors are used. $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ catalyzes the acetalization only in the presence of acid cocatalysts.[48] Best results are achieved in the conversion of styrene (**25**) to acetals **26** and **27** with use of pyridinium *p*-toluenesulfonate (PPTS) as cocatalyst (eq 8).



Lower regioselectivities but high enantioselectivities are reported in hydroformylation of styrene (**25**) with the catalyst system [(−)-BPPM]Pt($SnCl_3$)Cl in the presence of triethyl orthoformate. The ratio of the products **26** and **27** is determined as 1:2 with an enantiomeric excess of >96% for the branched acetal **26**.[49] The acetal formation prevents racemization of the aldehyde product. Similar results are obtained with 2-ethenyl-6-methoxynaphthalene (**28**). The acetal **29** of the branched hydroformylation product is an intermediate in the synthesis of naproxen (**30**) (eq 9). With norbornene the ee of 60% is lower than with terminal olefins.[49]



With $[Rh(\mu\text{-}SCR_2CH(NH_3)(COOH)]_2[OTf]_2$ (R = H, R = Me) as catalysts no additional acid cocatalyst is needed; the ammonium salt present gives an acidic pH.[50] These catalyst precursors convert simple olefins, e.g. 1-octene, or terpenoids (e.g. isolimonene (**31**) or *β*-pinene) with high chemoselectivity (eq 10). Conversion of *(−)-β*-pinene gives similar results with 87:13 diastereoselectivity at the newly created stereogenic center.

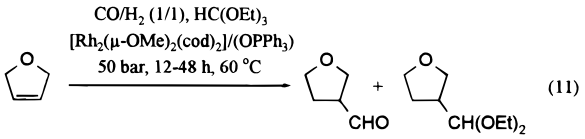


["Rh"] = $[Rh(\mu\text{-}SCMe_2CH(NH_3)(COOH)]_2)(OTF)_2]$

In comparison, the classical catalyst HRh(CO)-$[P(OPh)_3]_3$ only allows 31% conversion of isolimonene

(**31**) forming a mixture of 50% aldehyde and 50% acetal (**32**).[50]

Acetal formation as described above can also be employed to functionalized alkenes. The rate of the hydroformylation/acetalization sequence of 2,5-dihydrofuran (**33**) to give **35** depends on the acid added. PPTS allows complete conversion of the intermediate aldehyde **34** (eq 11).[48]

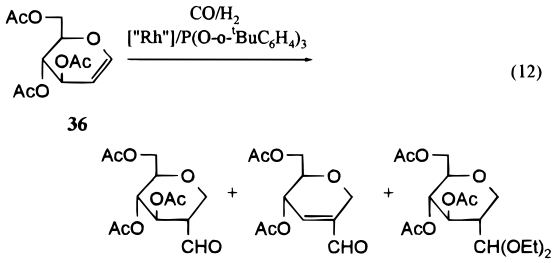


(11)

33 **34** **35**

cat.	-	96 %	4 %
	$SnCl_2$	26 %	1 %
	PPPTS	-	100 %

The same method if applied to 3,4,6-tri-*O*-acetyl-D-glucal (**36**) leads to the acetal **39** in 55% yield whereas in the absence of $HC(OEt)_3$ and/or PPTS elimination of AcOH from oxo aldehyde **37** to form the unsaturated aldehyde **38** is a major side product (eq 12).[51]



(12)

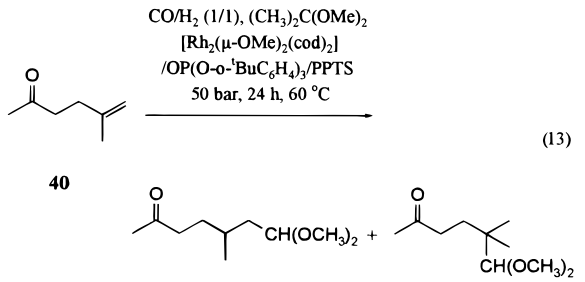
36

37 **38** **39**

with $HC(OEt)_3$/PPTS	6	11	55
with $HC(OEt)_3$ only	9	24	27
none	54	22	-

["Rh"] = $[Rh(\mu\text{-OMe})(cod)]_2$

The conversion of 5-methyl-5-hexen-2-one (**40**) in the presence of DMP exclusively leads to the dimethyl acetals **41** and **42** of both hydroformylation products (eq 13) with high *n*-selectivity and high aldehyde acetalization selectivity.[48]



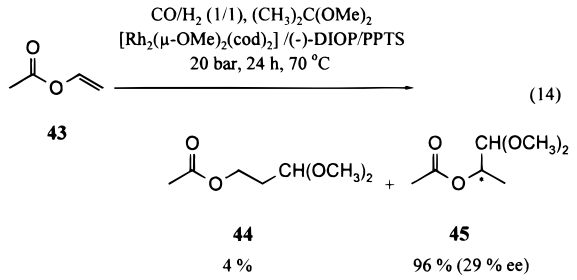
(13)

40

41 **42**

97 % 3 %

On the other hand vinyl acetate (**43**) gives the branched dimethyl acetal **45** as the major product. When the hydroformylation/acetalization sequence of vinyl acetate (**43**) is carried out with (−)-DIOP as chiral ligand, no significant improvement of the ee in comparison to the hydroformylation without PPTS is observed (eq 14), whereas the regioselectivity is



(14)

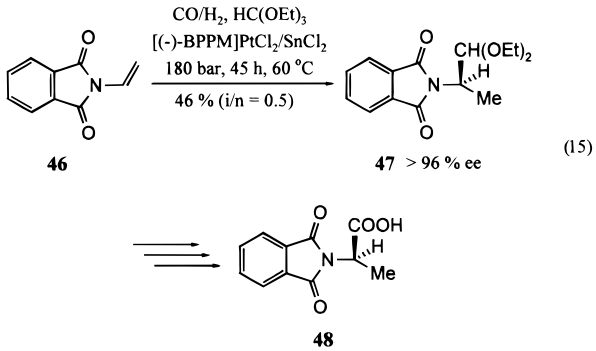
43

44 **45**

4 % 96 % (29 % ee)

increased from 20:80 to 4:96 with PPTS.[48] With the catalyst system [(−)-BPPM]$Pt(SnCl_3)Cl$ the regioselectivity decreases to 40:60 with a high increase of the enantioselectivity up to 98% ee.[49]

Asymmetric hydroformylation of unsaturated amines offers a pathway towards the synthesis of amino acid derivatives with high ee. To prevent racemization the conversion of *N*-vinylphthalimide (**46**) to *N*-phthalylalanine (**48**) can be performed via the acetal **47** with the catalytic system [(−)-BPPM]-$Pt(SnCl_3)Cl$ (eq 15).[49]



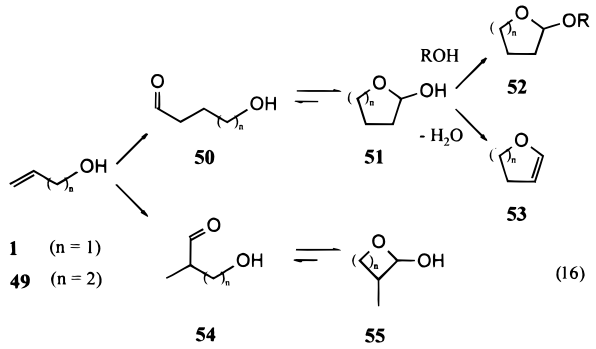
(15)

46 **47** > 96 % ee

48

B. Intramolecular Acetal Formation

Formation of cyclic acetals via a hydroformylation/acetalization sequence is expected if alkene compounds bearing a nucleophilic oxygen group are used. Thus aldehydes bearing a remote alcohol function spontaneously cyclize, especially if five- or six-membered rings can be formed. Consequently various unsaturated alcohols of type **1/49** form cyclic hemiacetals (lactols) **51/55**. By variation of the reaction conditions, subsequent conversions of the hemiacetals can be integrated in the one-pot sequence. Thus these hemiacetals give the corresponding enol ethers (e.g. **53**) after elimination or various acetals (e.g. **52**) if other alcohols are added (eq 16).[52]



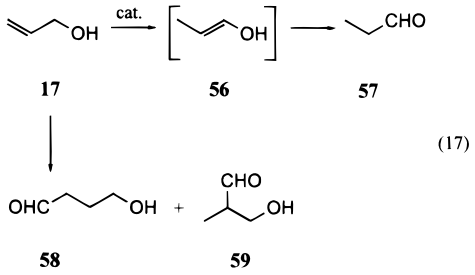
(16)

50 **51** **52** **53** **54** **55**

The products obtained by this type of tandem hydroformylation offer access to a wide range of interesting compounds. Hydrogenation of the hemiacetal leads to diols which are important precursors, e.g. for ethers and resins.[53] It is also possible to oxidize the lactols to lactones. Other reactions can be performed at the double bond of the enol ether (epoxidation, dihydroxylation, allylic substitution). These reactions enable the synthesis of subunits of naturally occurring products with biological and pharmacological activities.[54,55] The results described in this chapter are ordered according to the type of unsaturated alcohols used as starting material.

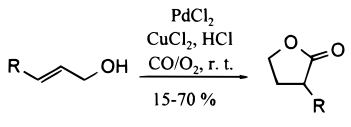
a. Allylic Alcohols

According to early investigations using cobalt catalysts, allylic alcohols give only small amounts of hydroformylation products while other unsaturated alcohols such as 4-penten-1-ol are hydroformylated to form the expected hydroxyaldehydes and products derived therefrom.[56,57] The main product in the conversion of the parent compound allylic alcohol (**17**) is propanal (**57**) generated by double-bond isomerization and tautomerization.[56,58] With phosphine-modified rhodium carbonyl catalysts this isomerization can be suppressed.[59]



(17)

Formation of lactones instead of hemiacetals can also occur under hydroformylation conditions. While with rhodium[56] and cobalt[60] catalysts, however, only small amounts of the lactones of type **61** are observed, selective lactone formation is observed with palladium catalysts.[61−67] Treatment of substituted allylic alcohols **60** with carbon monoxide, oxygen, copper(II) chloride, and hydrochloric acid in tetrahydrofuran containing palladium chloride affords furanones **61** (eq 18).[61−64]



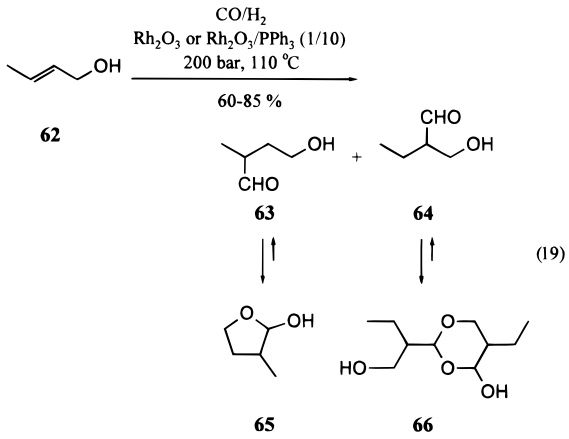
(18)

R = H, Me, Pr

With $[Pd_2(dba)_3]\cdot CHCl_3$ as catalyst the lactones **61** can be prepared without further additives. Numerous other lactone formations are reported[68−74] including use of chiral ligands producing optically enriched furanones.[66,67]

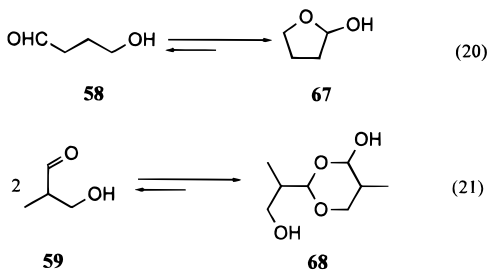
Control of the linear-to-branched ratio of the hydroformylation/lactol products **58** and **59** (eq 17) is effectively influenced by the catalytic system used, the carbon monoxide/hydrogen ratio, the pressure, and the temperature. These influences were studied in hydroformylation of allylic alcohol (**17**) with the phosphine-modified catalyst $HRh(CO)(PPh_3)_3$.[75] Variation of the rhodium/phophine ratio has only small effects on the linear/branched ratio. Similar effects are observed in the pressure range of 3.5−55 bar. With increase of the temperature the product distribution becomes more complex. The byproducts obtained are propanol and after isomerization propanal (**57**). An increase in the H_2/CO ratio from 0.1 to 10 results in an increase of regioselectivity with a factor of 4 in favor of the linear product **58**. Regioselectivity is also influenced by the ligands such as triphenylphosphine, tributylphosphine, triphenyl phosphite, tris(*p*-chlorophenyl) phosphite, 1,2-bis (diphenylphosphino)ethane, $(Ph_2PCH_2CH_2)_2PPh$, and 1,1′-bis(diphenylphosphino)ferrocene. The highest linear/branched selectivities at high conversion rates are achieved with 1,1′-bis(diphenylphosphino)ferrocene.[75]

Higher allylic alcohols such as 2-buten-1-ol (**62**), 3-methyl-2-buten-1-ol (**79**), 1-buten-3-ol (**71a**), and 2-methyl-3-buten-2-ol (**76a**) lead to different product types depending on their substitution pattern. Hydroformylation of **62** with unmodified rhodium catalyst gives hydroxyaldehydes with 60% yield while addition of tertiary phosphines increases the yields up to 85%.[56]



(19)

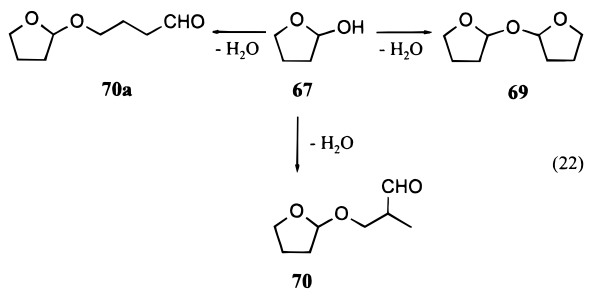
The hydroformylation products obtained are in equilibrium with their cyclic hemiacetals (e.g. **65**) or intermolecular acetalization products (e.g. **66**).[56] Similar behavior is observed with hydroxy aldehydes obtained via different procedures. Thus the hydrodroxy aldehyde **58** is known to undergo a ring closure in an equilibrium to form the intramolecular hemiacetal **67** (eq 20),[76] whereas the branched product **59** forms the dimer **68** by intermolecular cyclization (eq 21).[77]



(20)

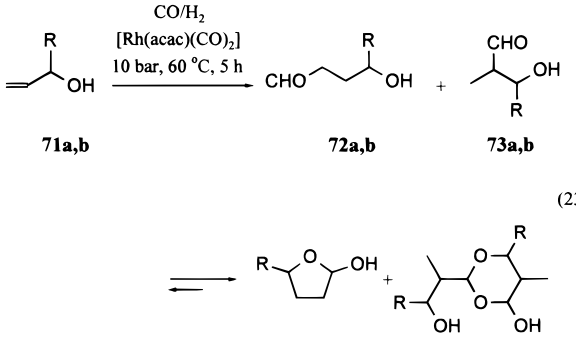
(21)

Other acetal products, such as **69** and **70** are observed due to condensation of the furanol **67** with the open chained hydroxyaldehydes **58** and **59** or with itself (eq 22).[78]



70a **67** **69** **70** (22)

Allylic alcohols of type **71** bearing a secondary alcohol function in the allylic position again lead to cyclization products of type **74** and **75** (eq 23) with



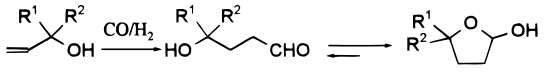
71a,b **72a,b** **73a,b** (23)

74a,b **75a,b**

a R = CH_3	L: $Ph_2P(CH_2)_4PPh_2$	100 %	-
	PPh_3	100 %	-
	$P(O\text{-}m\text{-}MeC_6H_4)_3$	37 %	63 %
	$P(O\text{-}m,m'\text{-}Me_2C_6H_3)_3$	54 %	46 %
	$P(O\text{-}o\text{-}Me_2C_6H_4)_3$	100 %	-
	$P(OPh)_3$	100 %	-
b R = C_5H_{11}	L: PPh_3	100 %	-
	$P(OPh)_3$	81 % (+ 19 % **72b**)	-

regioselectivities depending on the type of the phosphine ligands added. With the catalyst system Rh(acac)$(CO)_2$ the addition of triphenylphosphines, triphenyl phosphites, or diphosphines $Ph_2P(CH_2)_xPPh_2$ (x = 2, 4) has only minor effects on the regioselectivity. 3-Buten-2-ol (**71a**) with these systems exclusively gives the cyclic furanol **74a**. Only with *meta*-methylated triphenyl phosphites, due to a higher catalyst reactivity, but lower regioselectivity, the dimer **75a** derived from the branched hydroformylation product is also detected (eq 23).[39] Noteworthy, 1-octen-3-ol (**71b**) exclusively gives the linear hydroformylation product **74b**.[39] Surprisingly, the unsubstituted triphenyl phosphite in the hydroformylation reaction of **71b** effects the formation of a 19:81 mixture of cyclic and open chain products **72b** and **74b** while with other ligands only the cyclic product **74b** is obtained.[39]

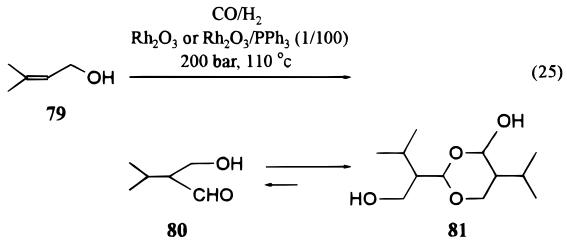
Compounds including tertiary alcohol functions in the allylic position (e.g. **76a**−**d**) selectively give the *n*-hydroformylated products **77a**−**d**, which form the lactols **78a**−**d** after intramolecular cyclization. With unmodified rhodium or cobalt catalysts the hemiacetal **78a** is obtained in good yields. With rhodium oxide/triphenylphosphine as the catalyst system the lactol **78a** forms acetals of the type **69**.[56] Linalool (**76b**) containing an additional highly substituted double bond is exclusively hydroformylated in the less substituted position. As the sole product, the cyclic hemiacetal **78b** is observed.[52] Larger alkyl substituents can inhibit the cyclization. Thus the open chain hydroxy aldehyde **77c** results from the conversion of isophytol (**76c**).[56] Aromatic substituents in allylic position are also tolerated in the reaction sequence. 1,1-Diphenyl-prop-2-en-1-ol (**76d**) gives the furanol **78d** in 84% yield.[79]



76a-d **77a-d** **78a-d** (24)

a	$R^1 = R^2 = CH_3$	Rh_2O_3, 200 bar, 110 °C	see text
b	$R^1 = CH_3$, R^2 = 	$RhHCO(PPh_3)_3/PPh_3$ (1/760), 75 bar, 3 h, 100 °C	86 %
c	$R^1 = CH_3$, $R^2 = i\text{-}C_{16}H_{33}$	Rh_2O_3, 200 bar, 110 °C	see text
d	$R^1 = R^2 = Ph$	$[Rh(OAc)_2]_2/PPh_3$ (1/4), 60 bar, 20 h, 60 °C	84 %

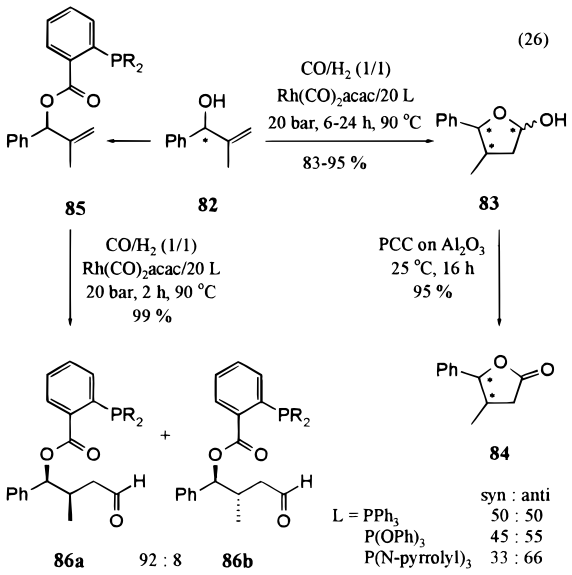
Prenyl alcohol (**79**) with a terminally disubstituted double bond is selectively hydroformylated in the iso-position to form aldehyde **80** which cyclizes to form the acetal **81**.[56]



79 **80** **81** (25)

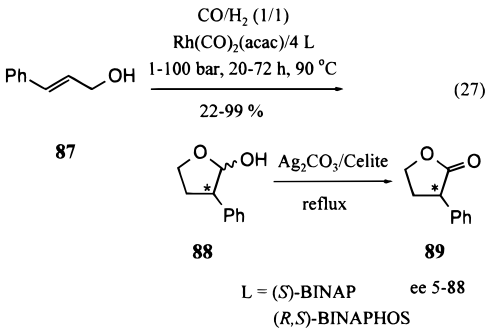
Hydroformylation of substituted allylic alcohols leads to new stereogenic centers. This is of synthetic interest also in subsequent hemiacetal/lactone formation. Usually, only low stereoselecitvities are observed. This however can be influenced by additional ligands and/or stereocontrolling substituents within the substrate. Thus, if using achiral phosphorus ligands in hydroformylation of the allylic alcohol **82** only low diastereoselectivities of the lactol **83** are observed. Lactol **83** is oxidized to lactone **84** in order to determine the ratio of the diastereomers.[80,81] With triphenylphosphine a 1:1 ratio of the *syn*/*anti*-diastereoisomers of lactone **84** is determined. On changing to triphenyl phosphite and to tripyrrolylphosphane, an increase in the amount of the *anti*-product up to 2:1 is observed (eq 26).

If, however, the ligands are attached to the OH groups of substrates of type **82**, effective stereocontrol is observed leading to open-chain normal hydroformylation products.[80,81]Thus hydroformylation of **82** is performed via the *ortho*-diphenylphosphanyl benzoate **85**. This catalyst-directing group enables the selective formation of the corresponding *syn*-alde-



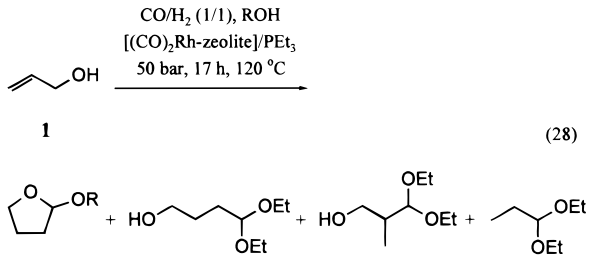
hydes **86a**. Similar effects are observed with the corresponding homoallylic alcohols.[82]

Rhodium-catalyzed enantioselective lactol synthesis via tandem hydroformylation/acetalization of cinnamyl alcohol (**87**) is achieved with chiral ligands such as *(S)*-BINAP, *(R)*-2-NAP-BIPNITE, and *(R,S)*-BINAPHOS.[83] The ee's were determined from the lactones obtainable via oxidation. The best results are obtained with *(R,S)*-BINAPHOS (eq 27).



Hydroformylation of other allylic alcohols [e.g. **1**, **62**, **42** (R = Me, Et)] under similar conditions gives linear/branched product ratios depending on the substitution pattern with lower ee's than in the conversion of **87**.[83]

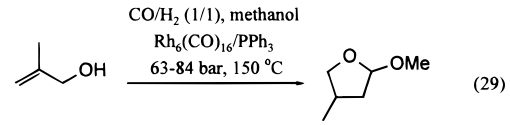
Use of heterogeneous instead of homogeneous catalyts is of great interest for industrial applications of these methods. Immobilizing homogeneous transition metal complexes onto solid supports offers advantages in catalyst separation and reuse and avoids loss of the precious metal during workup.[19] Silica,[84] polystyrene,[75] and zeolites[37] are used as supports. Silica-supported rhodium catalysts are prepared by impregnation of silica with $HRh(CO)(PPh_3)_3$ and a phosphorus ligand. These catalyst systems allow conversion of allylic alcohol (**1**) to the furanol **67** in a continuous gas-phase reaction.[84] Polymer-supported catalyst systems lead to a small increase in the linear/branched ratio in hydroformylation of allylic alcohol (**1**). The influence of the other reaction conditions resembles that of homogeneous rhodium catalysts.[75] Using zeolite-encapsulated rhodium carbonyls in the hydroformylation of allylic alcohol (as already described above), intra- and intermolecular acetalization products are obtained. The initial products **58**, **59**, and **67** as well as propanal (**57**), which is the isomerization product of allylic alcohol (**1**), lead to acetals upon further conversion of the hemiacetal (lactol) with the alcohol solvent. The regioselectivity of the reaction depends on the nature of the zeolite; lower cation loadings (higher Si/Al ratios) enhance the formation of the cyclic acetal **90**.[37]

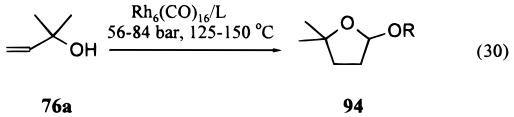


		90a	18	19	91
ROH = EtOH:	zeolite: X	62 %	10 %	28 %	-
	Y	32 %	3 %	4 %	15 %
	ZSM 5	60 %	10 %	20 %	10 %

Cyclic acetals of the type **90** can also be synthesized in the presence of alcohols and homogeneous rhodium carbonyl catalysts with addition of a cocatalyst.[85] While with triphenylphosphine in methanol only 45% dimethyl acetal **90b** is obtained, the yield of **90b** is enhanced up to 60% with triphenylarsane or triphenylphosphine and *o*-phthalic acid (Table 1).[53]

Substituted allylic alcohols of type **92** and **76a** give high yields of cyclic acetals due to the higher regioselectivities in this process (eqs 29 and 30).[53,85]





L: PPh_3, R : Me	94 %
L: Ph_3As, R : Pr	90 %
L: PPh_3/o-phthalic acid, R: ^{t}Bu	85 %

b. Open Chain Homoallylic Alcohols

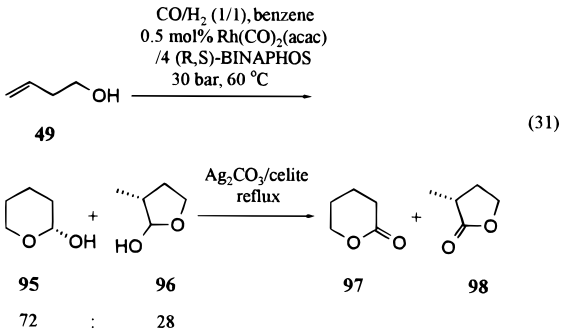
With application of the hydroformylation/acetalization sequence to homoallylic alcohols, both the branched and the linear products can undergo ring closure reaction according to the scheme above (eq 16). The linear product forms tetrahydropyran derivatives, whereas the branched aldehyde leads to tetrahydrofuran derivatives.

Using the parent homoallylic alcohol (**49**), both cyclic hemiacetals **95** and **96** are obtained. Asym-

Table 1. Cyclic Acetals via Hydroformylation of Allyl Alcohol in the Presence of Diols

entry	solvent ROH	catalyst	pressure (bar)	temp (°C)	yield (%)	**90**
1	CH_3OH	$Rh_6(CO)_{16}/PPh_3$	20−35	125−150	45	**90b**
2	CH_3OH	$Rh_6(CO)_{16}/Ph_3As$	63−84	130−135	53	**90b**
3	CH_3OH	$Rh_6(CO)_{16}/PPh_3$/phthalic acid	56−84	115	60	**90b**
4	$CH_3CH_2CH_2OH$	$Rh_6(CO)_{16}/Ph_3As$	63−84	125	48	**90c**
5	$(CH_3)_2CHCH_2CH_2OH$	$Rh_6(CO)_{16}/Ph_3P$/phthalic acid	56−84	125	49	**90d**

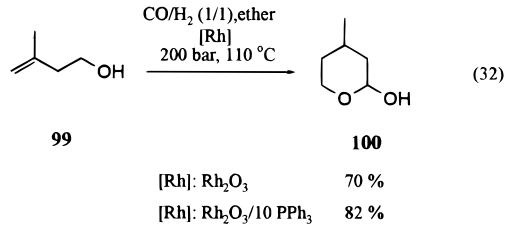
metric hydroformylation of **49** with $Rh(acac)(CO)_2$ and *(R,S)*-BINAPHOS gives the products **95** and **96** in a 72:28 ratio (eq 31). This linear/branched ratio is



similar to that of 1-hexene, suggesting that the hydroxyl group has no effect on the reaction rate and selectivity in this case. The ee (73% ee for 3-(*R*)-**96**] is much better than in the corresponding conversion of allylic alcohol (**17**).[83]

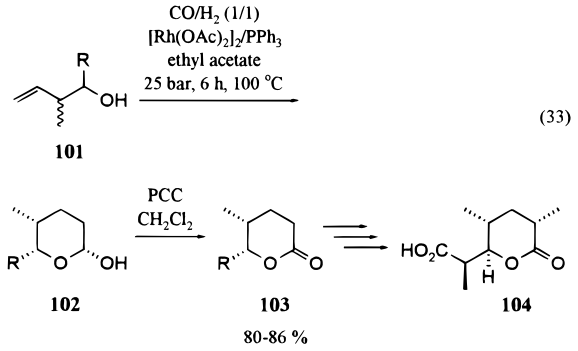
Lactones such as **97** and **98**, which are prepared in a subsequent oxidation,[83] can also be synthesized by direct hydrocarboxylation in the presence of cobalt carbonyl catalysts. Especially, substituted homoallylic alcohols lead to the five- and six-membered lactones.[60]

When homoallylic alcohols carry substituents in the internal position of the double bond, only the linear products are observed. Thus hydroformylation of 3-methyl-3-buten-1-ol (**99**) with rhodium oxide as catalyst leads to 2-hydroxy-4-methyl-tetrahydropyran (**100**) in 70% yield. With triphenylphosphine-modified rhodium catalysts the yield increases to 82% due to the suppression of isomerization (eq 32).[56]

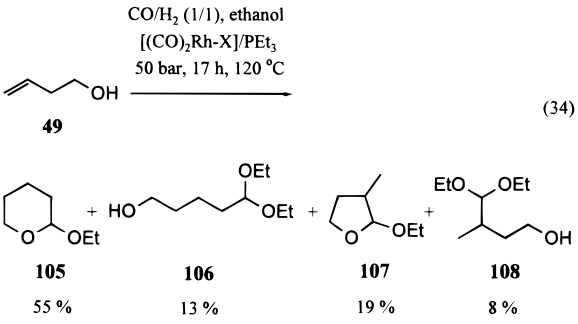


The same reaction can be performed with the rhodium carbonyl catalysts containing $Ph_2P(O)H$, $(n\text{-}C_8H_{17})_2P(O)CH(OH)Pr$, and Ph_2POEt at lower pressures.[86] The stereochemistry of hydroformylation/lactol formation of homomethallylic alcohols is effectively controlled by *ortho*-diphenylphosphanyl benzoyl groups attached to the hydroxyl group.[82]

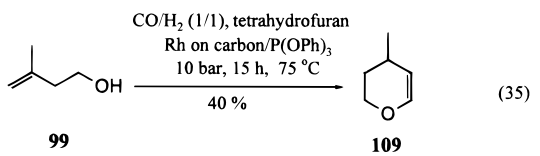
These reaction sequences offer access to interesting building blocks of natural products.[54,87−89] A representative example is the synthesis of the pyranone subunit of the Prelog−Djerassi lactone **104**. For this purpose various 1,2-disubstituted homoallylic alcohols of type **101** are hydroformylated with $[Rh(OAc)_2]_2$/triphenylphosphine (eq 33).[90]



Condensation of the primary hemiacetal products with alcohols leading to acetals can also be included into the hydroformylation/acetalization sequence. Analogous to eq 28 the unsubstituted homoallylic alcohol **49** in alcohol solution leads to intra- and intermolecular acetal formation (**105**−**108**) with zeolite-encapsulated rhodium catalysts (eq 34).[37]

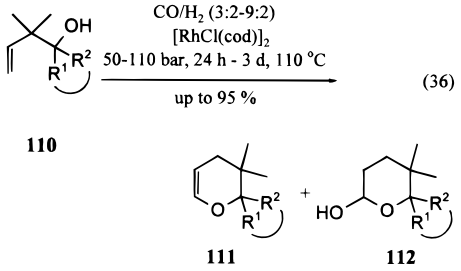


With rhodium on carbon as solid support the dehydration of the cyclic hemiacetals to cyclic enol ethers can be integrated in the process of hydroformylation/acetalization. With 3-methyl-3-buten-1-ol (**99**) the 3,4-dihydro-4-methyl-2*H*-pyran (**109**) is obtained with 54% selectivity (eq 35).[91] In comparison with this reaction the homogeneous mode (eq 32) results in the formation of only the tetrahydropyranol (see above).[56]



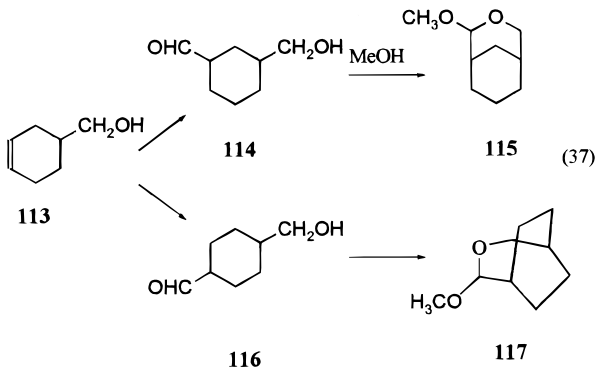
This version can be applied to the synthesis of spiropyrans as potential precursors for pheromones or antibiotics.[54,87] Hydroformylation of the homoallylic alcohols **110** with quaternary centers both in allylic and homoallylic position selectively leads to the *n*-hydroformylated products forming the spiropyran derivatives **111** and **112** under the reaction

conditions. The cyclic system in the homoallylic position can vary in the ring size. Substituents or heteroatoms in the rings are also tolerated (eq 36).[92]

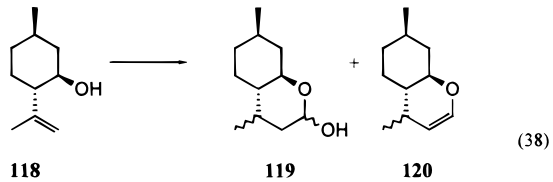


c. Other Unsaturated Alcohols

Using cyclic unsaturated alcohols the formation of bicyclic acetals with different ring size is observed after the one-pot hydroformylation/acetalization sequence. When the reaction is carried out with the alcohol **113**, a mixture of both regioisomeric hydroformylation products **114** and **116** is formed and further leads to the cyclization products **115** and **117** (eq 37).[93]



Similar transformations of cyclic monoterpenes offer access to valuable intermediates in organic synthesis. Thus, isopulegol (**118**) leads to partially hydrogenated chromane derivatives.[52,94] Variation of the reaction conditions results in different products. With the catalyst system $RhH(CO)(PPh_3)_3/PPh_3$ only the lactol **119** is obtained via intramolecular cyclization.[52] With dinuclear thiolato-bridged rhodium precursors either the lactol **119** or the corresponding dehydrated enolic ether **120** is observed (eq 38).[94]

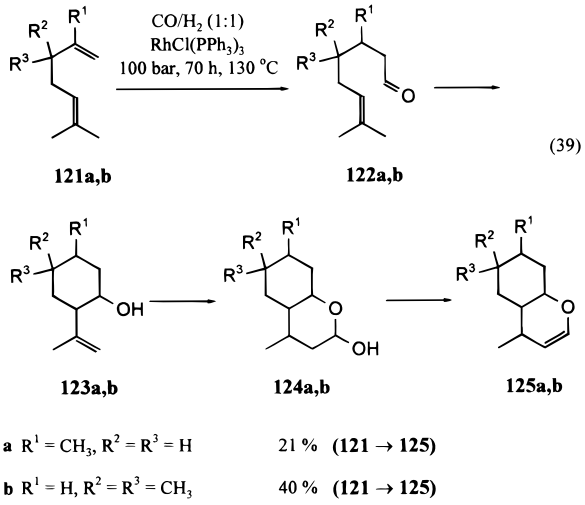


$[Rh(\mu\text{-}S^tBu)(CO)(P\{OPh\}_3)]_2$ 13 bar CO/H_2, 16 h, 78 °C	79 %	5 %
$[Rh(acac)(CO)_2]$/3 $P(OPh)_3$ 30 bar CO/20 bar H_2, 20 h, 80 °C	6 %	40 %
$[RhCl(PPh_3)_3]$ 50 bar CO/50 bar H_2, 20 h, 120 °C	—	59 %

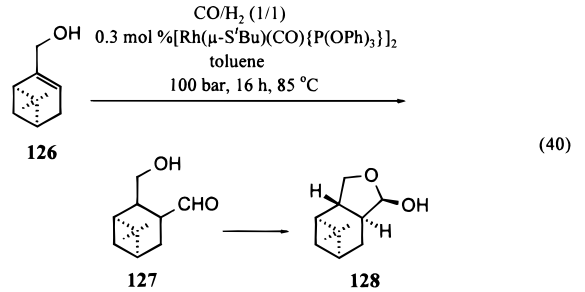
The dinuclear thiolato-bridged rhodium catalyst allows diastereoselective reactions of optically pure isopulegol (**118**). A diastereoselectivity of 60−64% in favor of one diastereoisomer is achieved. This reaction gives higher selectivities than conversions performed with DPPB, DPPH, or the chiral phosphine DIOP.[94]

The yield of enolic ether **120** can be enhanced by using the rhodium catalyst precursor $Rh(CO)_2(acac)$/triphenyl phosphite. Higher temperatures also support the dehydration. With $[RhCl(cod)]_2$ and the Wilkinson catalyst the yield of **120** is increased up to 59%, but the selectivity of the hydroformylation process is generally lower.[95]

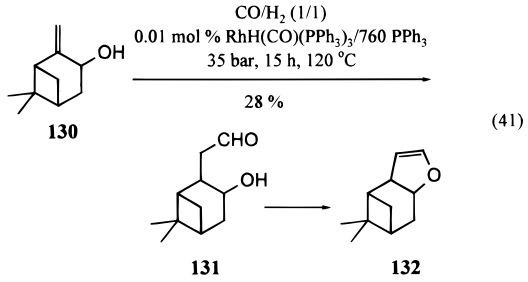
Wilkinson's catalyst allows the synthesis of hydrogenated chromane derivatives of type **125** even if starting from the corresponding 1,5-dienes **121**.[95] In this four step reaction hydroformylation of the terminal double bond, metal-induced carbonyl-ene reaction,[96,97] and hydroformylation/acetalization of the cyclic alcohol are combined in a one-pot reaction sequence (eq 39).[95]



If the same procedure is applied to (−)-myrtenol (**126**), the tricyclic tetrahydrofuranol derivative **128** is isolated. It is assumed that the cyclization of the hydroxy aldehyde **127** takes place after the hydroformylation process during chromatographic purification (eq 40).[94]

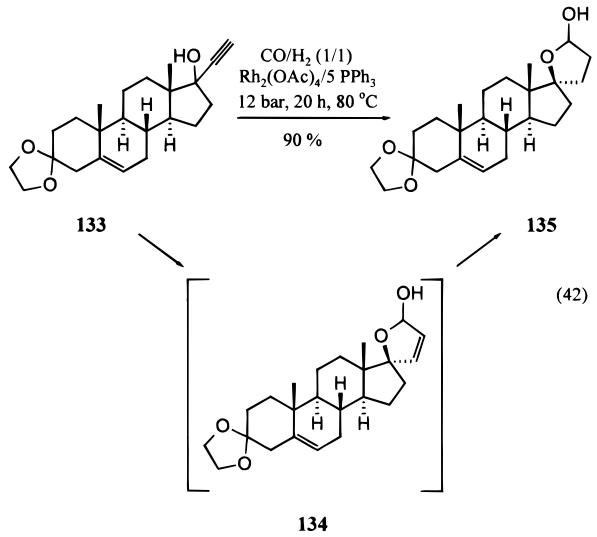


Similarly pinocarveol (**130**), a bicyclic alcohol with an exocyclic methylene group, can be hydroformylated to the hydroxy aldehyde **131**. In addition to this product, the bicyclic enol ether **132** is formed via cyclization and dehydration (eq 41).[52]



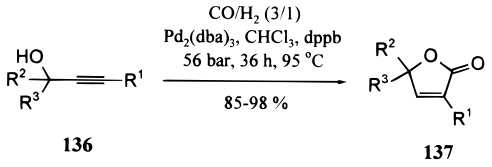
(41)

When alkynols are used in hydroformylation sequences of this type, tetrahydrofuranols are formed. This reaction is applied in the synthesis of spironolactones.[98] In this case a hydrogenation of the dihydrofuranol **134** is integrated in the sequence (eq 42).



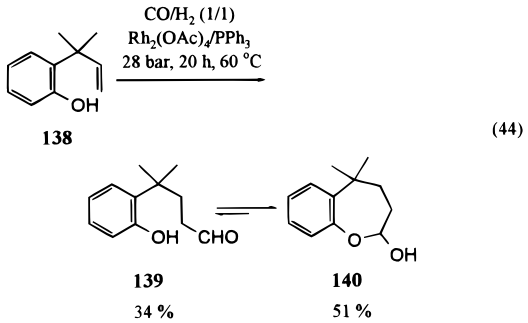
(42)

In contrast to rhodium systems other catalysts, especially Pd complexes, lead to unsaturated furanone derivatives **137** if converting propargylic alcohols of type **136** under hydroformylation conditions (eq 43).[99] Numerous other examples of this type are reported.[100,101]



(43)

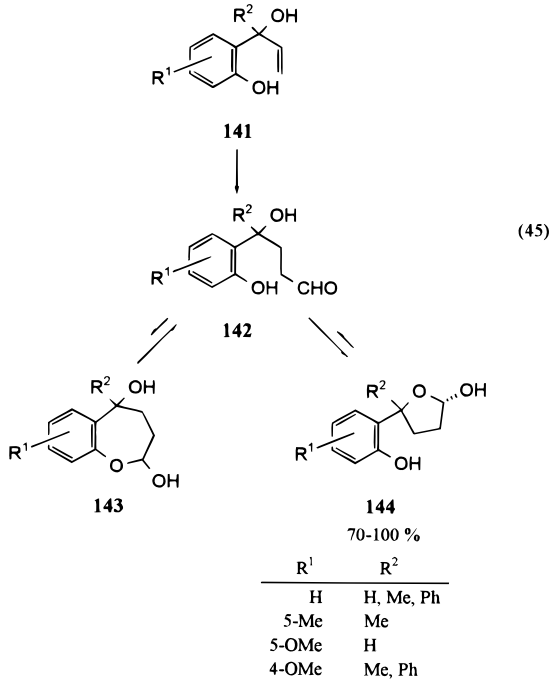
Benzopyrans and benzooxepines can be prepared by hydroformylation of phenols with unsaturated side chains. Thus hydroformylation of 2-(2-hydroxyphenyl)-2-methyl-3-butene (**138**) gives only the linear



(44)

aldehyde **139**, which is in equilibrium with the benzoxepine derivative **140** (eq 44).[79]

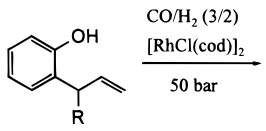
Ortho-substituted unsaturated phenols with additional hydroxy groups in an allylic position like **141** can form lactols via two different reaction pathways; however, only the five-membered ring **144** is observed. Obviously the five-membered ring is more stable than the seven-membered ring **143** (eq 45).[79]



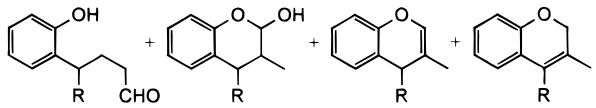
R^1	R^2
H	H, Me, Ph
5-Me	Me
5-OMe	H
4-OMe	Me, Ph

(45)

Benzopyran derivatives are obtained from the branched hydroformylation products of allylic phenols of type **145**. By employment of the hydroformylation/acetalization sequence on these allylic phenols **145a,b**, the open chain linear aldehydes **146** and the cyclic chromane derivatives **147**−**149** are obtained. Dehydration of the lactol **147** can be promoted at higher temperature or under acidic conditions, however, with lower selectivities[102] (eq 46).

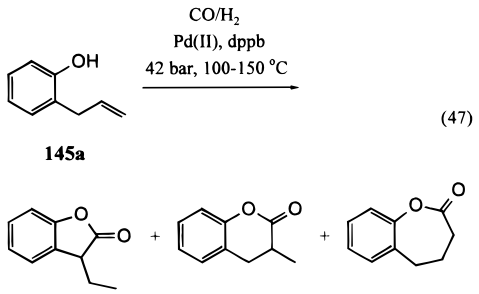


(46)

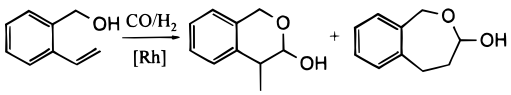


			146	147	148	149
a	R = H	$[RhCl(cod)]_2$ 20 h, 110 °C	38 %	51 %	-	-
		$[RhCl(cod)]_2$ /o-phthalic acid 20 h, 150 °C	15 %	6 %	16 %	14 %
b	R = Me	$[RhCl(cod)]_2$ 20 h, 120 °C	43 %	-	14 %	-

If a similar conversion of allylic phenol **145a** in the presence of Pd catalysts is performed, seven-membered ring **152** and five-membered ring lactones **150** are obtained in addition to six-membered ring formation to **151**[103] (eq 47).

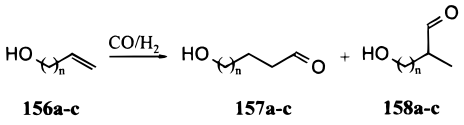


Isobenzopyran derivatives can be synthesized from (2-vinylphenyl)methanol (**153**). With this alcohol the six-membered ring **154** and seven-membered ring product **155** are generated in good yields. Variation of the catalysts suppresses the formation of the seven-membered lactol **155**[102] (eq 48).



CO/H_2 (30/20bar) $[RhCl(cod)]_2$ 20 h, 110 °C	42 %	36 %
CO/H_2 (30/20bar) $Rh(acac)(CO)_2$ 20 h, 60 °C	52 %	-
CO/H_2 (30/20bar) $Rh(acac)(CO)_2$ 20 h, 80 °C	59 %	27 %

Larger heterocyclic rings cannot be prepared by intramolecular acetalization of the hydroformylation products of α,ω-unsaturated alcohols. 5-Hexen-1-ol (**156a**, $n = 4$),[39] 9-decen-1-ol (**156b**, $n = 8$), and 10-undecen-1-ol (**156c**, $n = 9$)[104] give only the hydroxy aldehydes **157a−c** and **158a−c** (eq 49).



a n = 4
b n = 8
c n = 9

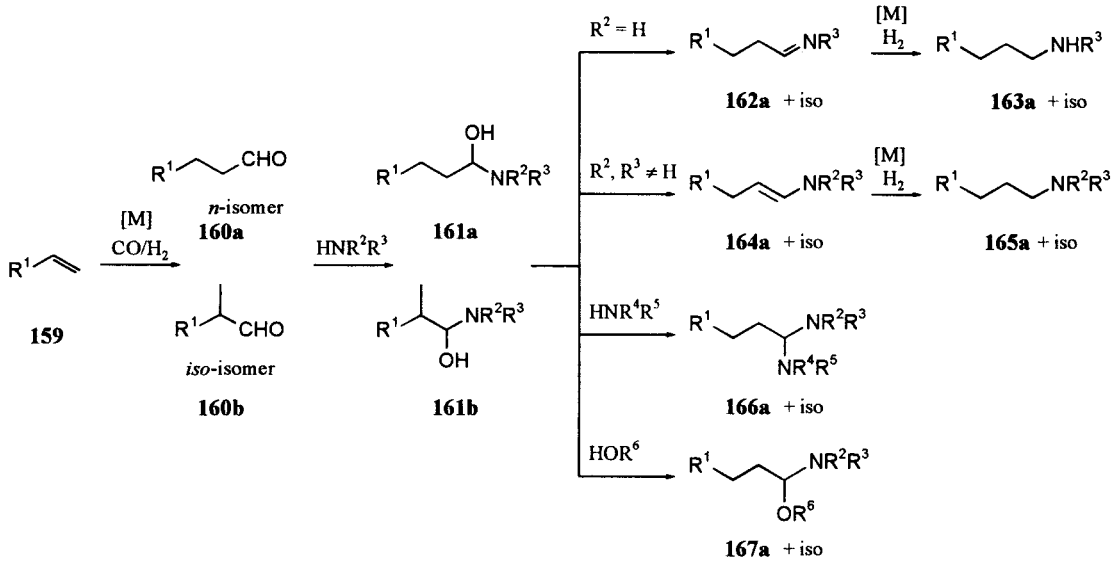
IV. Tandem Hydroformylation in the Presence of N-Nucleophiles

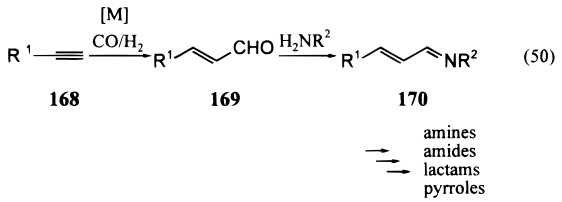
The reaction of aldehydes with nitrogen-containing compounds, e.g. amines, is well-known in organic synthesis. The generation of the aldehydes via metal-catalyzed hydroformylation of olefins **159** in the presence of amines allows a tandem hydroformylation to form aldehydes with subsequent addition of N-nucleophiles leading to a variety of nitrogen products (Scheme 3). The first two steps in these reaction sequences are common: formation of the regioisomeric aldehydes **160a,b** as the first step and addition of an amine to yield the O,N-semiacetal **161a,b** in a second step. If ammonia or primary or secondary amines are used, imines **162a,b** or enamines **164a,b**, respectively, can be generated via subsequent dehydration. These can be converted in a final hydrogenation step to primary, secondary, or tertiary amines **163** or **165**. Alternatively, depending on the substrate and the reaction conditions, N,N- and O,N-acetals **166** and **167** can be formed.

All reactions described in Scheme 3 can also be performed in intramolecular versions if unsaturated amines are used. Similar reaction sequences can be applied to alkynes **168,** leading to amines, amides, lactams or pyrroles (eq 50).

If summarized, hydroformylation in the presence of amines may lead to a versatile range of nitrogen products. The following material is arranged according to product type.

Scheme 3

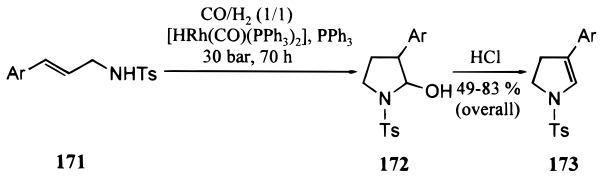




(50)

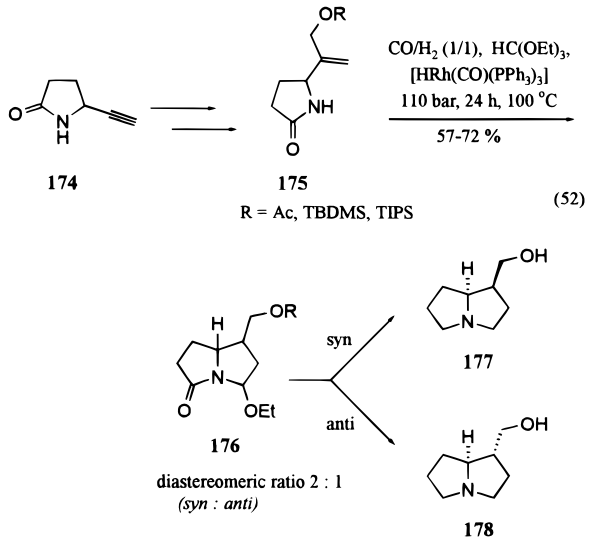
A. Synthesis of O,N-Acetals

The transition metal catalyzed transformation of unsaturated amines offers a convenient synthetic access to cyclic O,N-acetals. These compounds are reactive and synthetically attractive building blocks for various cyclic O,N-acetals, including pharmaceuticals and natural products, such as alkaloids. Thus tosylated and aryl-substituted allylic amines **171** under hydroformylation conditions lead to O,N-semiacetals **172** as isolable species. Upon dehydration dihydropyrroles **173** are obtained in good overall yields (eq 51).[105]



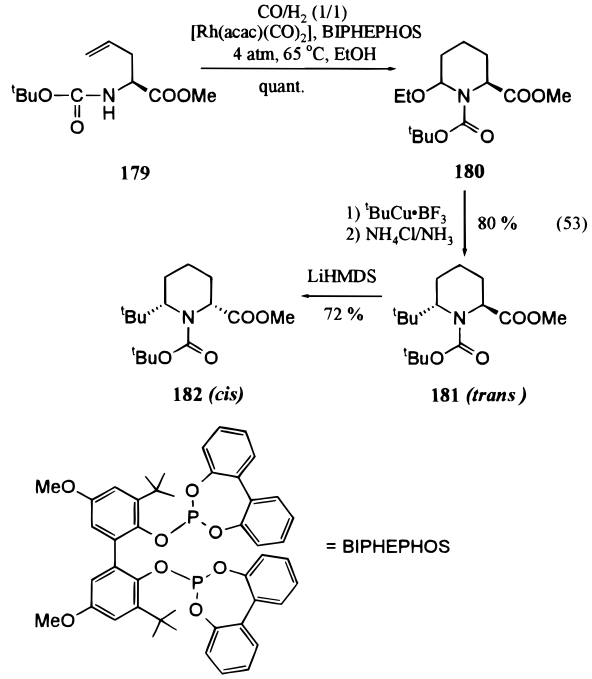
(51)

In the presence of ortho esters hydroformylation of allylic amides leads to O,N-acetals. This method is used for the construction of the basic skeleton of pyrrolizidine alkaloids, an 1-aza-bicyclo[3.3.0]octane ring system.[106] The allylic amides **175** (generated from alkyne **174**) under typical hydroformylation conditions in the presence of $HC(OEt)_3$ give the corresponding O,N-acetals **176** in moderate up to good yields (eq 52). Further conversion of the syn and anti diastereoisomers lead to the alkaloids (±)-isoretronecanol (**177**) and (±)-trachelanthamidine (**178**).[106]



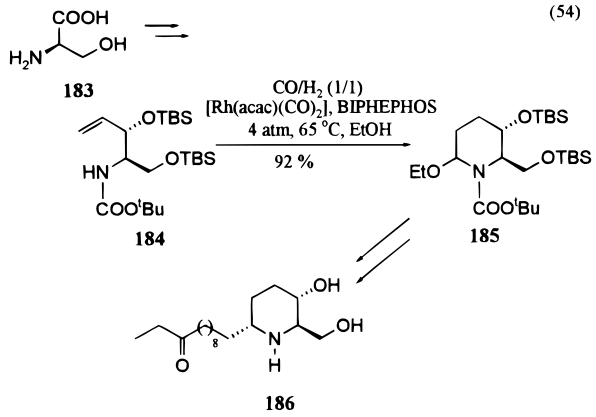
(52)

Treatment of optically active allyl glycinate **179** with catalytic amounts of $Rh(acac)(CO)_2$−BIPHEPHOS in the presence of syngas and alcohols results in exclusive formation of piperidine **180**. Conversion of the O,N-functionality in **180** with $^tBuCu{\cdot}BF_3$ proceeds with excellent diastereoselectivity to give solely the trans product **181**. The *cis*-isomer of **182** is formed by epimerization at C-2 (eq 53). These piperidines as pipecolic acid derivatives have proved to be versatile key intermediates in the synthesis of izidine alkaloids.[107]



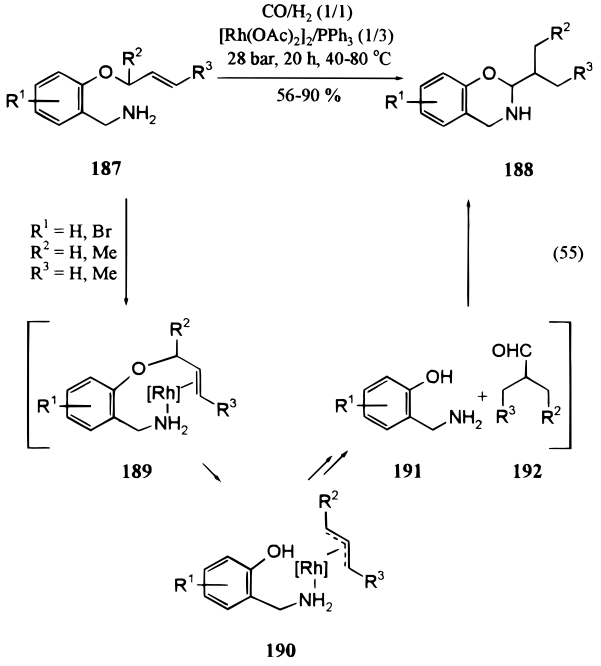
(53)

In a similar sequence the synthesis of (+)-prosopinine (**186**) starting from enantiopure D-serine (**183**) as a key step requires the construction of the O,N-acetal **185** which is effectively achieved via regioselective Rh-catalyzed cyclohydrocarbonylation of **184** (eq 54).[108]

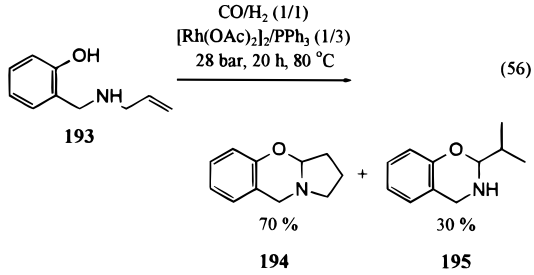


(54)

Reactions of 2-(allyloxy)benzylamines **187** with syngas in the presence of a rhodium(I) catalyst give 1,3-benzoxazines **188**. By cross-over experiments these reactions have been shown to include allylic cleavage followed by regioselective carbonylation at the internal carbon of the resulting allyl rhodium species **190** and condensation of the aldehyde **192** thus formed with the amino alcohol fragment **191** (eq 55).[109,110]

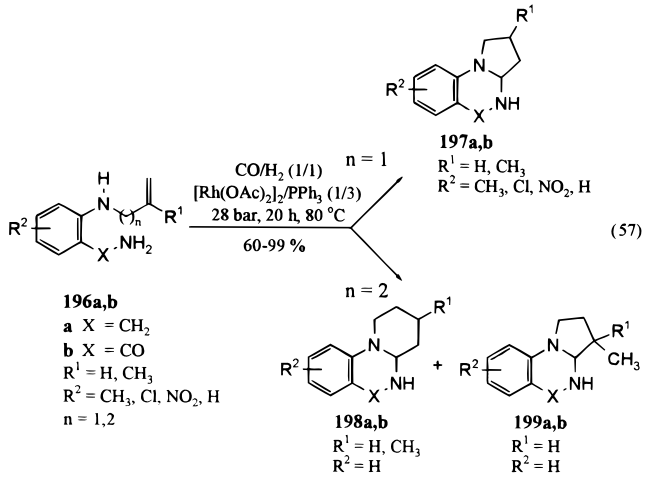


Similarly the reaction of 2-(*N*-allylaminomethyl)-phenol (**193**) with syngas under hydroformylation conditions leads to a mixture of pyrrolo[2,1-*b*]benz-oxazine (**194**) and of oxazine **195** (eq 56).[109]

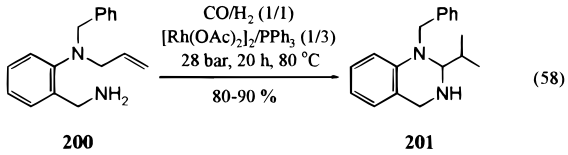


B. Synthesis of N,N-acetals

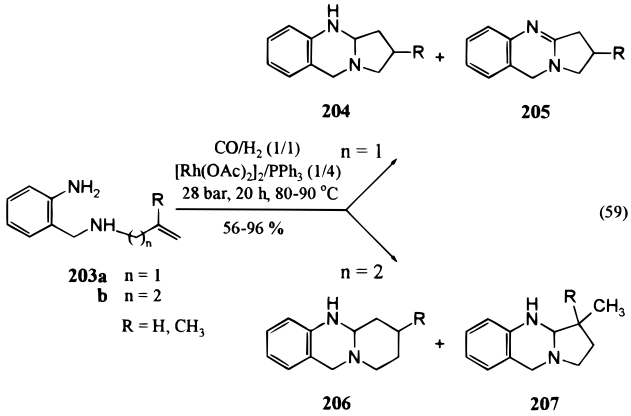
Similar to O,N-acetals, corresponding N,N-acetals are obtainable if a second N-nucleophile is present. Rhodium-catalyzed reactions of *ortho*-(alkenylamino)-benzylamines **196a** or -benzamides **196b** with syngas in excellent yields give quinazolines **197a**−**199a** and quinazolinones **197b**−**199b** containing a fused ali-cyclic ring (eq 57). This one-pot synthesis in the first step includes hydroformylation and proceeds with condensation of the amino/amido groups.[111] If allylic amines are used, only the *n*-hydroformylation is preferred and the aldehyde products undergo ring closure to form quinazolines or quinazolinones **197a,b**. With homoallylic substrates two reaction pathways are observed resulting in a mixture of five- and six-membered N,N-acetals **198** and **199**. If electron-withdrawing groups are attached to the aromatic system, increased amounts of noncyclized iso-hydro-formylation products are obtained.[112] With other diamines the formation of amidines is observed.[113,114]



In contrast to diamines **196a** the N-benzyl ana-logue **200** under similar conditions leads to the tetrahydroquinazoline **201** (eq 58) including an allylic cleavage as described above (eq 55).[109]



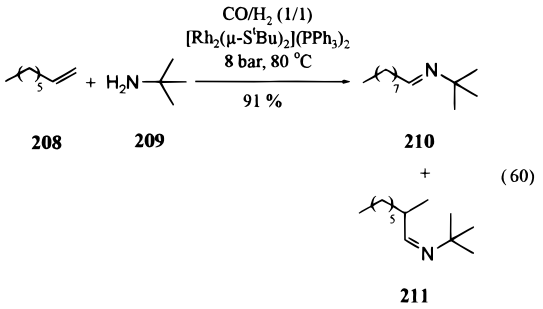
The quinazolines and quinazolinones thus obtained have a wide range of biological activities and are cur-rently marketed as pharmaceutical agents. In anal-ogy allylic diamines without a fused aromatic ring system can also be cyclized by the one-pot sequence described above.[115,116] Similar results are achieved if *ortho*-amino-*N*-alkenylbenzylamines **203a,b** are con-verted under hydroformylation conditions (eq 59).[117]



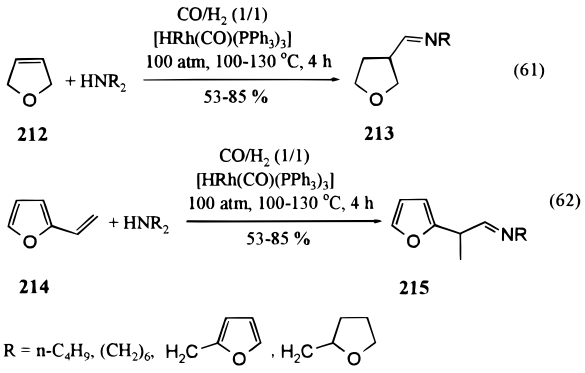
C. Synthesis of Imines

The hydroformylation of olefins in the presence of primary amines offers access to imines. Usually these intermediates suffer hydrogenation in a subsequent step (see Scheme 3). Thus only a limited number of examples of selective imine formation via hydro-formylation in the presence of amines are described. So $[Rh_2(\mu\text{-S-}^t\text{Bu})_2(CO)_2(PPh_3)_2]$ catalyzes hydroformy-lation followed by an amine condensation reaction sequence of 1-octene (**208**).[118,119] Only with bulky amines such as *tert*-butylamine (**209**) imines such as **210** and **211** can be isolated (eq 60). Otherwise hydrogenation of the carbon−nitrogen double bond to form saturated amines takes place (see chapter below).

Furane derivatives **212** and **214** and primary amines under hydroformylation conditions are con-

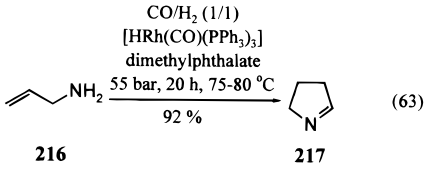


verted to the imines **213** and **215** (eqs 61 and 62).

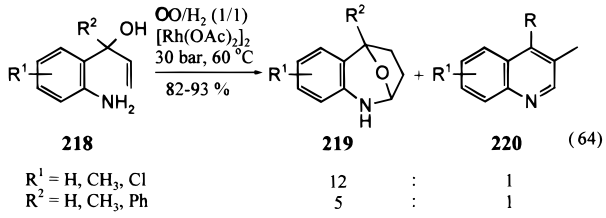


With 2-vinylfurane (**214**), similar to styrene, mainly imine **215** resulting from iso-hydroformylation is generated. This regioselectivity is attributed to electronic effects (eq 62).[120,121] Noteworthy, secondary amines under similar conditions lead to hydrogenated tertiary amines (see chapter below).

The parent allylic amine **216** in an intramolecular hydroformylation/condensation reaction sequence in the presence of $[HRh(CO)(PPh_3)_3]$ is converted to dihydropyrrole **217** in 92% yield (eq 63).[57] Usually, however, allylamines under hydroformylation conditions give β-lactams (see below).



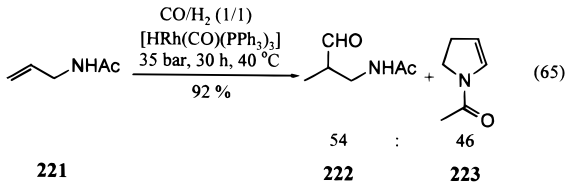
Pharmacologically interesting benzazepines **219** arise from allylic amino alcohols **218** via hydroformylation and an intramolecular condensation with the amino group. The iso-product eliminates water to generate the aromatic quinoline system **220**, whereas the heterocycle **219** arising from the *n*-products does not undergo this elimination (eq 64).[79,122]



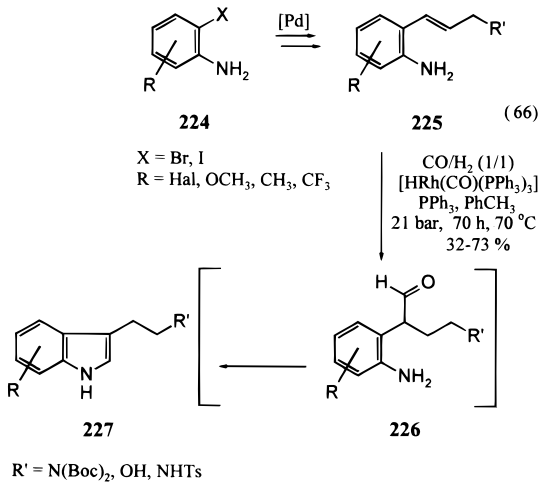
In the absence of a hydroxy group of **218** ($R^1 = R^2 = H$), in modest yields the corresponding imine and the aromatic system **220** is observed in an 1:1 ratio.[79]

D. Synthesis of Enamines

Hydroformylation in the presence of secondary amines usually leads to enamines. With primary amines these are only favored if the enamine unit is part of a conjugated or aromatic system. Acylated primary amines lead to enamides (acyclated enamines). Thus *N*-acetylallylamine **221** under typical hydroformylation conditions yields the iso-product **222**, whereas the *n*-product undergoes cyclization to form the enamide **223** (eq 65).[123] The preferred formation of the iso-product **222** is typical in hydroformylation of heterosubstituted allylic systems.[124]

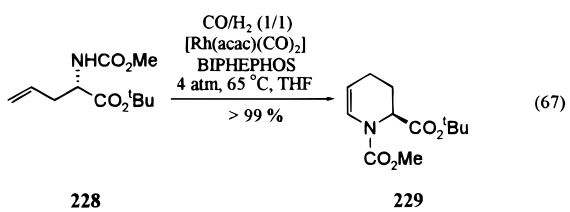


A similar reaction sequence is effectively applied to the synthesis of substituted indols **227**, e.g. tryptamine derivatives.[125] Via Heck reaction *ortho*-haloanilines **224** are converted to *ortho*-vinylanilines **225** which cyclize to indols **227** in a hydroformylation/condensation sequence in moderate up to good yields (eq 66).[125] The observed substituted tryptamines and



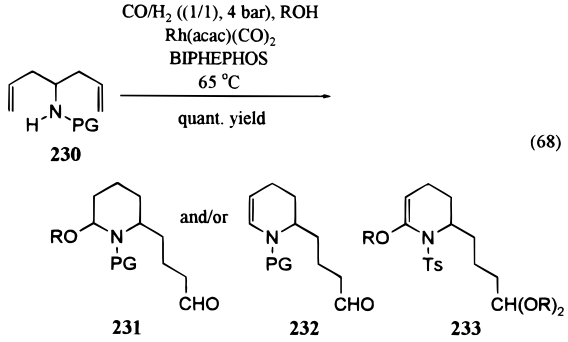
tryptophols **227** are common structural units in indole alkaloids with important pharmacological properties. A similar formation of indenes has been achieved starting from *o*-nitrostyrenes.[126] Here the sequence starts with a reduction of the nitro group under hydroformylation conditions.

The cyclohydrocarbonylation of 2-(alkoxycarbonyl)-4-pentenoate **228** in the presence of $[Rh(acac)(CO)_2]$ under syngas atmosphere in THF selectively leads to the corresponding pipecolic acid **229** in quantitative yield (eq 67).[107,108] In contrast to the unmodified



catalyst systems the selectivity toward *n*-hydroformylation is achieved by addition of BIPHEPHOS. It is noteworthy that the reactions under these conditions yield O,N-acetals instead of enamines, if alcohols are used as solvent (eqs 53 and 54).[107,108]

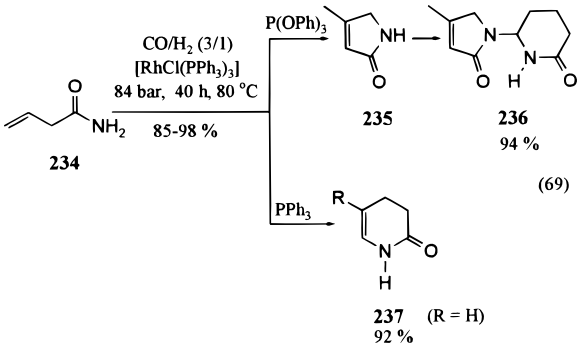
Depending on the reaction time and the solvent protected diolefinic amines, **230** undergoes an analogous reaction sequence leading to O,N-hemiacetals **231**, enamines **232**, or O,N-ketene−acetals **233**, respectively (eq 68).[127] Short reaction times selec-



(68)

tively lead to **231** whereas with extremely prolonged reaction times enamines **232** are generated in quantitative yields. For alcohols as solvents N,O-ketene−acetals **233** are observed in high yields.[127]

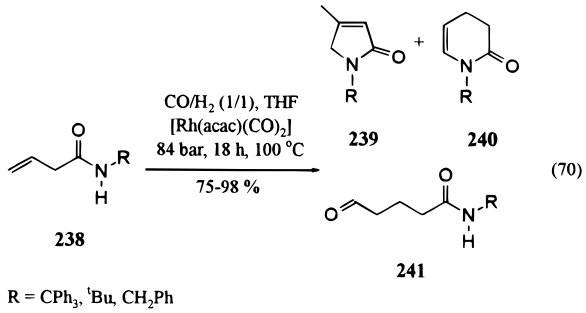
Primary alkenamides **234** undergo a hydroformylation/amidocarbonylation reaction sequence followed by a hydrogen shift. Depending on the ligands applied, two different types of products are obtained (eq 69).[128] In the case of PPh_3 the enamide **237** is



(69)

generated whereas $P(OPh)_3$ directs to the heterodimer **236**, resulting from a rhodium-catalyzed crossed coupling of the five- and six-membered N-heterocycles **235** and **237** arising from both iso- and *n*-hydroformylation. Here the monocyclic heterocycles are only minor products. It should be noted that solely the cross-coupling product **236** and no homocoupling product is observed. If the carbon chain of **234** is extended by one CH_2 group, exclusively a six-membered heterocycle of type **237** is generated via an iso-hydroformylation. A seven-membered system or coupling products are not detected.[128]

In contrast to the primary alkenamides **234**, secondary alkenamides **238** under similar conditions react to form a mixture of unsaturated γ- and δ-lactams **239** and **240**. 3-Butenamides **238** bearing bulky substituents on the amide nitrogen undergo amidocarbonylation leading predominantly to the pyrrolinone **239** in the case of iso-hydroformylation and to an uncyclized aldehyde **241** remaining from *n*-hydroformylation (eq 70).[128]



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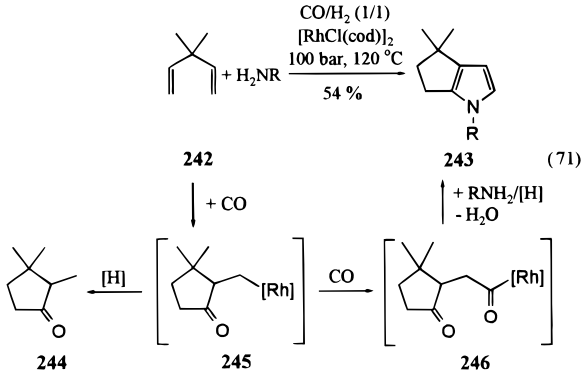
Enamines formed via hydroformylation can undergo further hydroformylation.[128] Reactions of this type are discussed in chapter IV of this article.

3,3-Dimethylpentadiene is transformed to the bicyclic pyrrol **243** via a double hydrocarbonylative cyclization/amine condensation sequence in medium yields (eq 71).[129] As a byproduct the cyclopentanone

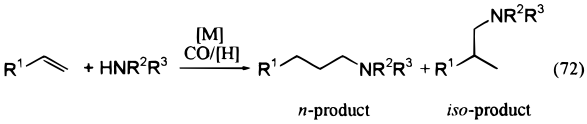


(71)

244 is observed, which is the major product in the absence of an amine.[130,131] Both products may stem from the same intermediate **245**. While **244** results from direct hydrogenolysis, the pyrrole **243** is formed via a second carbonylation and subsequent amine condensation of an 1,4-dicarbonyl intermediate.

E. Synthesis of Amines via Hydroformylation/Reductive Amination (Hydroaminomethylation)

Hydroformylation of alkenes in the presence of amines can lead to an overall "hydroaminomethylation" if the initial hydroformylation of an alkene is followed by the condensation of the intermediate aldehyde with a primary or secondary amine to form an enamine or imine, respectively, and a final hydrogenation to give a saturated secondary or tertiary amine (see Scheme 3, above, and eq 72). This reaction type has been reviewed only in brief and in connection with normal hydroformylation[8,28,132,133] or hydroamination.[134]



(72)

a. Hydroaminomethylation of Normal Alkenes

First examples of the hydroaminomethylation procedure were reported in 1943[135,136] and 1947.[137] Iron

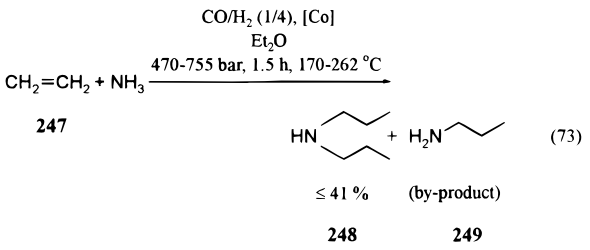
Table 2. Hydroaminomethylation of Various Olefins with Iron and Cobalt Catalysts

entry	alkene	amine	catalyst	T (°C)	p_{syngas} (bar)	yield[a] (%)	lit.
1	ethylene	piperidine	$Fe(CO)_5$	170	0	61	143
2	C_{10} up to C_{13} *n*-olefins	dimethylamine	$Co_2(CO)_8/PBu_3$	180−214	77−130	30−48	145
3	1-propene	morpholine, pyridine	$Co_2(CO)_8$/dppe	165−180	100	47−89	146
4	cyclohexene, 1-dodecene, 1-tetradecene	pyrrolidine, dimethylamine	$Fe(CO)_5/Rh_2O_3$	170	140	90−94	149, 150
5	1-pentene	piperidine	$Rh_6(CO)_{16}/Fe_3(CO)_{12}$, $Fe_3(CO)_{12}/Ru_3(CO)_{12}$	150	55	*b*	151, 152

[a] Yield of hydroaminomethylation products. [b] No yields given.

pentacarbonyls were used as catalysts or mixtures of these with the metals molybdenum, manganese, zinc, nickel, and copper, which are activated by heating to 350 °C under an ammonia and hydrogen atmosphere. Under severe reaction conditions (up to 390 °C, up to 950 bar) basic alkenes (ethene, propene, etc.) are converted in low yields.[138−142] The amounts of catalyst added reached to almost a stoicheiometric ratio. More recently,[143] however, the iron pentacarbonyl catalyzed hydroaminomethylation was optimized to give yields up to 61% (Table 2, entry 1). In the absence of additional CO pressure ethylene is converted with piperidine to *N*-propylpiperidine in the presence of 20 mol % iron pentacarbonyl. In a side reaction hydroamination to *N*-ethylpiperidine is observed.[143]

As shown above, iron carbonyl catalysts are rather inefficient in the hydroaminomethylation sequence and have therefore been replaced by cobalt-based systems. The first example of cobalt-catalyzed hydroaminomethylation of ethylene with ammonia leads to di-*n*-propylamine (**248**) and propylamine (**249**).[144] Thus overall dialkylation of ammonia prevails over monoalkylation.



To apply milder reaction conditions, phosphine-modified $Co_2(CO)_8$ is used for the reaction of various aliphatic 1-alkenes with secondary amines. The pressure can be reduced to 77−130 bar (Table 2, entries 2 and 3).[145,146]

The one-pot synthesis of primary amines, however, with low selectivities is achieved in the presence of Co/P-catalysts by reaction of 1-alkenes with ammonia and syngas. In the case of 1-hexene (**250**) the major products are primary C_7-amines **252a,b** and C_{14}-amines **254** (Scheme 4). The latter is generated via base-catalyzed aldol condensation of the in situ generated aldehydes.[133,147]

Only recently selective formation of primary amines via hydroformylation/reductive amination in the presence of ammonia has been achieved with a Rh/Ir catalyst system under two-phase conditions.[148]

Cobalt-catalyzed hydroaminomethylation leads to large amounts of byproducts such as formamides, amides, hydrogenation products, and especially alcohols. Therefore cobalt was replaced by other transition metals. The first attempts in this direction have been reported in 1971 making use of rhodium catalysts.[149] This metal was used in combination with iron pentacarbonyl. Simple olefins are converted with secondary amines in excellent yields (Table 2, entries 4 and 5).[149−152]

Over the last two decades rhodium or ruthenium catalyst have turned out to be more efficient than cobalt or iron. Rhodium systems catalyze hydroaminomethylation of normal terminal double bonds (such as small or long chain 1-alkenes or styrenes) and internal double bonds. Almost every type of primary and secondary amines is tolerated leading selectively to the corresponding secondary or tertiary amines in good up to excellent yields. The regioselectivities observed are comparable to those of the

Scheme 4

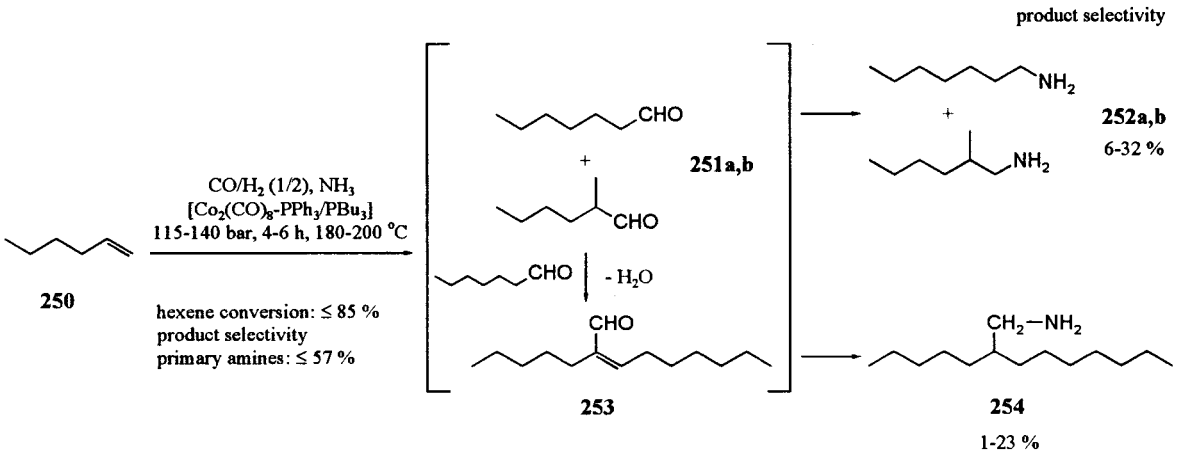


Table 3. Hydroaminomethylation with Rhodium Catalysts

entry	alkene	amine	catalyst	T (°C) (t (h))	p_{syngas} (bar)	yield[a] (%)	lit.
1	ethylene	*tert*-butylamine	$[RhCl(CO)_2]_2$	100 (1)	50	75	157
2	ethylene	octylamine	$[RhCl(CO)_2]_2$	110 (1)	50	68	157
3	ethylene	dipropylamine	$[RhCl(CO)_2]_2$	115 (1.5)	50	67	157
4	propylene	dibutylamine	$[HRh(CO)(PPh_3)_3]$	121 (0.5)	63	10	158
5	1-hexene	dimethylamine	$[Rh(CO)_2Cl(p\text{-toluidine})]$	150 (5)	120	98	159
6	1-hexene	dibutylamine	$[Rh(CO)_2Cl(p\text{-toluidine})]$	150 (1)	120	98	159
7	1-hexene	piperidine	$[Rh(CO)Cl(P(OPh)_3)_2]$	150 (3)	120	95	159
8	1-hexene	dimethylamine	$[RhCl(CO)_2]_2$	150 (2)	120	96	160
9	1-octene	diethylamine	$[Rh_2(\mu\text{-S-}^t\text{Bu})_2(CO)_2(PPh_3)_2]$	80 (15)	18	82[b]	118, 119
10	1-octene	morpholine	$[Rh_2(\mu\text{-S-}^t\text{Bu})_2(CO)_2(PPh_3)_2]$	80 (15)	8	55	118, 119
11	1-octene	*n*-butylamine	Ru(acac)$_3$/2,2′-bipy/pTsa	150 (1)	60	72	161
12	1-octene	1-aminoethan-2-ol	Ru(acac)$_3$/2,2′-bipy/*p*Tsa	130 (2)	60	55	161
13	1-octene	3-amino-2,2-dimethyl-propionic acid	Ru(acac)$_3$/2,2′-bipy/*p*Tsa	130 (10)	60	35	161
14	1-decene	dimethylamine	$Rh_6(CO)_{16}$	140 (6)	70[c]	65	162, 163
15	1-undecene	morpholine	$RhCl_3$	150 (3)	150	98	164
16	1-undecene	4-(aminomethyl)-piperidine	$RhCl_3$	150 (3)	150	96	164
17	1-dodecene	dimethylamine	Ru(acac)$_3$/Rh-2-ethyl-hexanoate	150 (5)	150	95	165
18	1-dodecene	morpholine	$[Rh(cod)Cl]_2$	80 (22)	110	100	166
19	1-dodecene	diethylamine	$RhCl_3 \cdot 3H_2O$	140 (3)	116	85	154
20	1-dodecene	L-proline ethyl ester	$[Rh(cod)Cl]_2$	90 (20)	110	84	167
21	1-dodecene	glycine ethyl ester	$[Rh(cod)Cl]_2$	110 (20)	110	81	167
22	1-tetradecene	L-prolinol	$[Rh(cod)Cl]_2$	100 (20)	100	98	167
23	1-tetradecene	L-valinol	$[Rh(cod)Cl]_2$	120 (20)	100	71	167
24	styrene	morpholine	$[Rh(cod)Cl]_2$	80 (22)	110	96	166
25	styrene	isopropylamine	$[Rh(cod)Cl]_2$	110 (22)	110	99	166
26	methylstyrene	morpholine	$[Rh(cod)Cl]_2$	80 (72)	110	97[d]	166
27	methylstyrene	*p*-anisidine	$[Rh(cod)Cl]_2$	110 (72)	110	95[d]	166
28	isobutene	pyrrolidine	Rh_2O_3	140 (6)	70[c]	70	162, 163
29	cyclohexene	morpholine	$[Rh(NBD)((CH_3)_2PPh)_3]PF_6$	140 (6)	70[c]	60	162, 163
30	cyclohexene	thiomorpholine	$Rh_6(CO)_{16}$	140 (6)	70[c]	55	162, 163
31	cyclohexene	piperazine	$[Rh(NBD)((CH_3)_2PPh)_3]PF_6$	140 (6)	70[c]	70	162, 163
32	2,5-dihydrofuran	diethylamine	$HRh(CO)(PPh_3)_3$	130 (5)	100	72	120
33	2-vinylfuran	piperidine	$HRh(CO)(PPh_3)_3$	100 (4)	100	85	121
34	triethylvinylsilane	morpholine	$[Rh(cod)Cl]_2$	80 (20)	100	56	168
35	N-vinylcarbazole	morpholine	$[Rh(cod)Cl]_2$	115 (20)	110	71	168
36	trimethylallylsilane	morpholine	$[Rh(cod)BPh_4]$	120 (20)	100	86	169
37	*N*-ethyl-N-methallylacetamide	morpholine	$[Rh(cod)Cl]_2$	110 (48)	110	95	169
38	*N*,*N*-diethylallylamine	diethylamine	$Rh_4(CO)_{12}$	100 (3)	90	40	170
39	methallyl ethyl ether	morpholine	$[Rh(cod)Cl]_2$	110 (48)	110	93	169

[a] Yield of all isomeric monohydroaminomethylation products. [b] *n*/iso = 40. [c] Only CO pressure. [d] Only *n*-product is obtained.

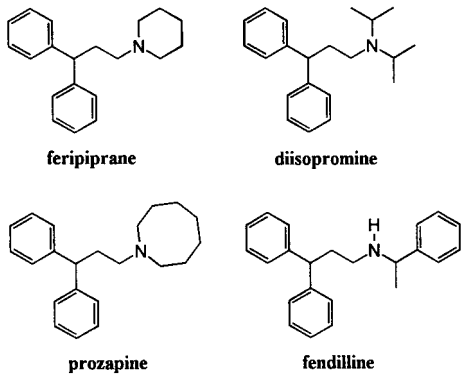
normal hydroformylation reactions.[153] For reasons discussed below primary amines are selectively monoalkylated, and in examples long chain 1-alkenes are used as substrates in the hydroaminomethylation procedure. The resulting products are useful for a variety of applications such as intermediates for emulsifiers, rust inhibitors, fabric softeners, finishing agents, insecticides, and bactericides.[154−156] The examples given in Table 3 represent typical reactions of those that have been described.

If the $[Rh_2(\mu\text{-S-}^t\text{Bu})_2(CO)_2(PPh_3)_2]$ catalyst[118,119] is used, the regioselectivity of the hydroaminomethylation due to steric hindrance of the catalyst turns out more *n*-selective than other common catalysts. Rh(I) 2-ethylhexanoate as a catalyst without bulky sulfur bridges also shows highly *n*-selective hydroaminomethylation; however, the yields are rather low and byproducts arising from aldol-type reactions predominantly stemming from the iso-product are generated.[165] These side reactions can be suppressed by addition of ruthenium complexes.[165] Substituted amines derived from α- or β-amino acids are also tolerated in the reaction sequence.[161,167] In the case of α-amino acid esters a surprising increase toward the iso-product is observed, indicating that the α-amino acid esters are acting as ligands in the catalytic system.[167] Use of optically active α-amino acid esters leads to partly racemized products with racemization occurring during the reaction sequence.[167] Several other substituted olefin systems have been investigated in hydroaminomethylation reaction (Table 3, entries 32−39) leading to the corresponding amines in good to excellent yields.

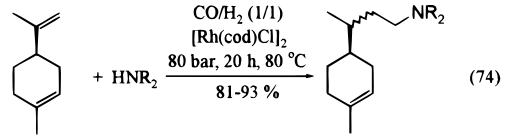
Various compounds of pharmaceutical interest such as the antiallergic and spasmolytic fenpiprane, the choleretic and spasmolytic diisopromin, the choleretic and spasmolytic prozapine, and the coronar dilator fendilline are easily available via hydroaminomethylation using 1,1-diphenylethylene as olefinic compound in good yields (Scheme 5). In a side reaction hydrogenation is observed, which can be suppressed by addition of PBu_3.[171,172]

Growth regulators for tobacco plants of type **257** are easily available starting from limonene (**255**) and secondary amines **256** in excellent yields compared to the classical two step procedure (eq 74).[177] The

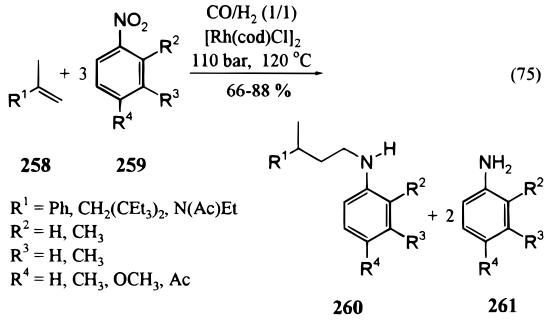
Scheme 5



internal double bond of limonene is not hydroaminomethylated for steric reasons.



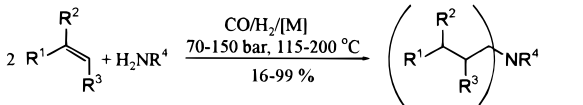
The scope of the hydroaminomethylation reaction sequence can be extended to nitro compounds acting as precursors for primary amines. Under typical hydroaminomethylation conditions these substrates are reduced to the corresponding anilines in a preceding step. This procedure offers further advantages with respect to the fact that aromatic nitro groups are the usual precursors of anilines. Thus several aromatic nitro compounds **259** are used in hydroaminomethylation of various olefins **258** leading to secondary or tertiary anilines **260** in good yields. Selective monoalkylation of the reduced nitrogen center is observed, if 3 equiv of the nitro compound is employed (eq 75).[173]



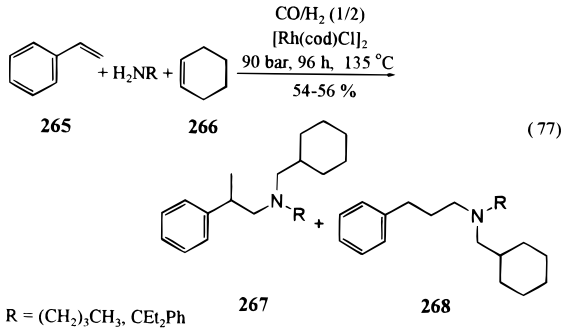
b. Bisalkylation of Amines via Hydroaminomethylation

One-pot methods with simultaneous and selective introduction of two identical or different alkyl substituents into an amine appear to be extremely difficult, if not impossible. For this problem the hydroaminomethylation protocol offers a straightforward solution. As the general reaction pathway (Scheme 3) shows, primary amines are transformed to imine intermediates. While imine formation is fast, hydrogenation of these imines is shown[174] to be slow. As a consequence, aldehydes generated by hydroformylation are completely consumed by the primary amine and with stoichiometric amounts of amine and olefin the secondary amine as the final product cannot be alkylated a second time.

On the other hand, however, selective bisalkylation of amines via hydroaminomethylation can be achieved if the in situ generated secondary amine is converted to a tertiary amine by alkylation with a second equivalent of olefin and the aldehyde formed thereof. In case of ammonia an analogous bis- or trishydroaminomethylation is observed (eq 76, Table 4; entries 2−6, 8). Similar to the monohydroaminomethylation (eq 75) the use of nitro compounds instead of primary amines is also possible (Table 4; entry 7).



Furthermore unsymmetrically substituted tertiary amines **267** and **268** can be generated, if two olefins are used which undergo hydroformylation with considerably different reaction rates as e.g. styrene (**265**) and cyclohexene (**266**) (Table 4; entry 8 and eq 77).[174]



c. Hydroaminomethylation of Diolefins and Polyolefins

α,ω-Diamines of type **270** with long aliphatic chains separating the two amino functions are of importance as synthetic and biological surfactants, membrane components, and bioactive compounds. A variety of these substances can easily be generated via hydroaminomethylation (Table 5 and eq 78).[161,167,177] In a similar way heterofunctionalized α,ω-diolefins are transformed to the corresponding diamines. Representative examples are spermine or spermidine analogues.[178]

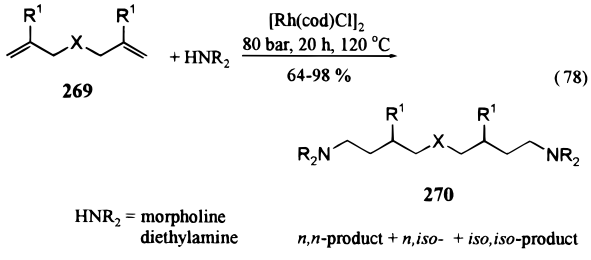


Table 4. Bisalkylation of Ammonia and Primary Amines

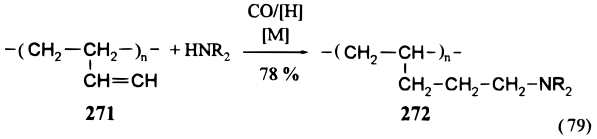
entry	alkene **262**	amine **263**	catalyst	T (°C) (t (h))	p_{syngas} (bar)	yield[a] of **264** (%)	lit.
1	cylohexene	ammonia	$Fe(CO)_5$/Raney−Co	200 (n.a.)	150	16[b]	175
2	cyclohexene	ammonia	Rh_2O_3	140 (6)	70[c]	50	162, 163, 176−180
3	cyclohexene	ammonia	$[Rh(cod)Cl]_2$	115 (96)	110	90	174
4	styrene	ammonia	$[Rh(cod)Cl]_2$	115 (24)	110	99	174
5	1-octene	ethylamine	$RhCl_3 \cdot 3H_2O$	140 (3)	98	81	154
6	α-methylstyrene	benzylamine	$[Rh(cod)Cl]_2$	135 (72)	90	91	174
7	α-methylstyrene	nitrobenzene	$[Rh(cod)Cl]_2$	135 (72)	90	88	173
8	styrene/cyclohexene	*n*-butylamine	$[Rh(cod)Cl]_2$	135 (96)	90	56[d]	174

[a] Yield of bishydroaminomethylated products. [b] Yield of trishydroaminomethylated products. [c] Only CO pressure. [d] Yield of unsymmetrical amine.

Table 5. Hydroaminomethylation of Diolefins

entry	alkene	amine	catalyst	T (°C) (t (h))	p_{syngas} (bar)	yield (%)	lit.
1	1,5-hexadiene	*n*-butylamine	$Rh(acac)(CO)_2$/$Ru(acac)_3$/2,2′-bipyridyl	130 (5)	60	80	161
2	1,5-hexadiene	*n*-butylamine	$Rh(acac)(CO)_2$/$Ru(acac)_3$/2,2′-bipyridyl	130 (2)	60	95	161
3	1,7-octadiene	diethylamine	$[Rh(cod)Cl]_2$	120 (20)	80	98	177
4	1,15-hexadecadiene	glycine ethyl ester	$[Rh(cod)Cl]_2$	110 (20)	110	85	167
5	1,7-octadiene	L-prolinol	$[Rh(cod)Cl]_2$	100 (20)	100	85	167
6	3,3-dimethylpentadiene	morpholine	$[Rh(cod)Cl]_2$	120 (20)	80	64	177
7	2,3-dimethylbutadiene	morpholine	$[Rh(cod)Cl]_2$	120 (20)	80	82	177
8	*N*-acetyldiallylamine	morpholine	$[Rh(cod)Cl]_2$	120 (20)	80	84	178
9	diallylic ether	morpholine	$[Rh(cod)Cl]_2$	120 (20)	80	83	178
10	*N*-acetylbis(methallyl)amine	morpholine	$[Rh(cod)Cl]_2$	120 (20)	80	89	178
11	bismethallyldimethylsilane	morpholine	$[Rh(cod)BPh_4]$	120 (48)	100	93	178

The hydroaminomethylation of each double bond of nonconjugated diolefins appears to occur independently one from another. Therefore the observed results resemble those of the monoolefins. Thus 3,3-dimethyl-1,4-pentadiene only leads to the *n*,*n*-product (Table 5; entry 6). In a similar manner polyolefins **271** and **273** can be converted to polyamines **272** or **274** (eqs 79 and 80).[179−181]



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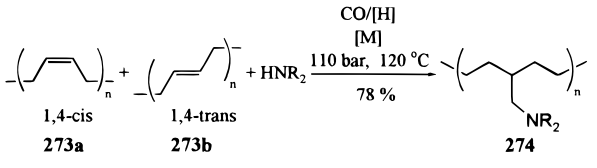
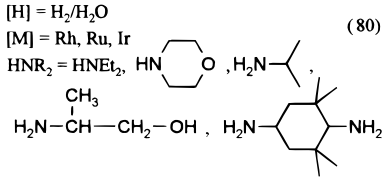
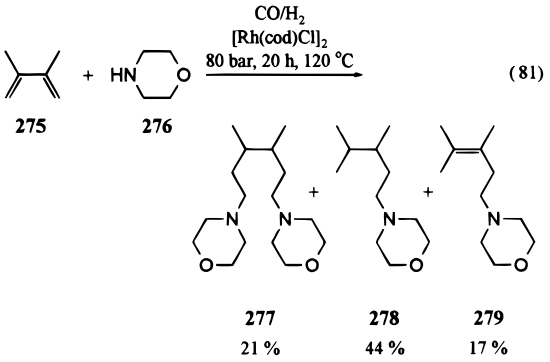




(80)

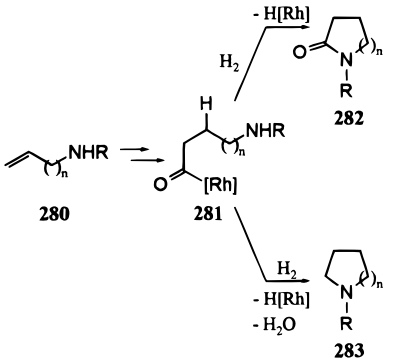
Conjugated diolefins usually undergo hydroformylation with low selectivities.[153] Often hydrogenation of at least one double bond occurs. Thus 2,3-dimethyl-1,3-butadiene (**275**) in the presence of morpholine (**276**) gives a mixture of the amines **277**−**279** (eq 81).[177]



(81)

d. Intramolecular Hydroaminomethylation of Unsaturated Amines

Unsaturated amines or amides **280** under hydroformylation conditions undergo intramolecular ring closure. The catalytic cycle of the hydroformylation offers two reaction pathways of the metal acyl intermediate **281** leading to lactams **282** on one hand or cyclic amines **283** on the other (eq 82).[3]



(82)

The generation of the lactams **282** proceeds via cleavage of the rhodium−acyl species **281** by the

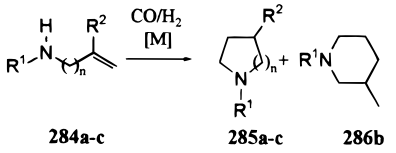
Table 6. Hydroaminomethylation of Allylic Amines

entry	substrate	catalyst	T (°C) (t (h))	p_{syngas} (bar)	yield (%)	lit.
1	phenylmethallylamine (**284a**, $R^2 = CH_3$)	$Rh(cod)BPh_4$	100 (30)	35[a]	84	195
2	phenylallylamine (**284a**, $R^2 = H$)	$Rh(cod)BPh_4$	100 (30)	35[a]	31	195
3	5-benzylamino-1-pentene (**284b**)	$HRh(CO)PPh_3$	100 (18)	124	85[b]	182
4	5-benzylamino-1-pentene (**284b**)	$HRh(CO)PPh_3/P(C_6H_{11})_3$	100 (18)	124	83[c]	182
5	methallylbenzamide (**284c**)	$[Co_2Rh_2(CO)_{12}]$	100 (18)	84	85	197

[a] Only CO pressure; $NaBH_4$/iso-PrOH as hydrogen source. [b] *n*/iso ratio = 5/95. [c] *n*/iso-ratio = 98/2.

nitrogen atom, which presumably is precoordinated to the metal.[182−184] Cyclic amines of type **283** are obtained from unsaturated amines if the intermediate **281** as an alternative undergoes hydrogenolysis by reaction with hydrogen. The aldehyde thus generated is following the hydroaminomethylation sequence to give **283** (eq 82). The chemoselectivity of these reactions is controllable by the ratio of syngas and/or the chosen ligand. An excess of hydrogen predominantly leads to the hydroformylation product, whereas in the presence of an excess of carbon monoxide the generation of lactams is preferred. Furthermore hydroformylation ratio is enhanced if alkylphosphine or alkyl phosphite ligands are used, whereas arylphosphines or aryl phosphites predominantly lead to the corresponding lactams.[115] Sterically highly hindered phosphite ligands such as BIPHEPHOS exclusively yield hydroformylation products. In addition, also the solvent influences the chemoselectivity.[57] On the other hand numerous examples of lactam formation are known.[31,36,57,103,115,182,185−196] These, however, are not generated via hydroformylation and therefore are not a topic of this review.

Intramolecular hydroaminomethylations to form five-, six-, or seven-membered cyclic amines are achieved if starting from arylmethallyamines **284a**,[195] alkenamines **284b**,[182,183] or methallylbenzamide **284c**[197] (eq 83). Conditions and catalysts are listed in Table 6.



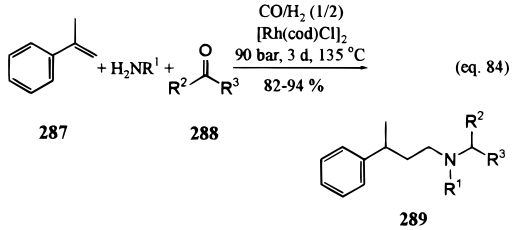
(83)

	R^1	R^2	n	Yield
a	Ar	CH_3, H	1	27-87
b	CH_2Ph	H	3	83-85
c	PhCO	CH_3	1	85

In the absence of a 2-methyl group in the allyl moiety the chemoselectivity is drastically decreased. Here the major byproduct (yield 33%) is an alcohol formed from iso-hydroformylation followed by direct hydrogenation. Furthermore hydrogenation of the starting material is observed (yield 10%). The amine **284b** according to the regioselectivity of the hydroformylation leads to six- or seven-membered cyclic amines. Phosphine ligands suppress iso-hydroformylation, and thus, the seven-membered ring **285b** is obtained as the major product.[182]

e. Hydroaminomethylation of Functionalized Olefins

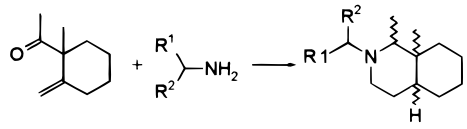
The unsymmetrical bisalkylation of primary amines has already been discussed above (eq 77). This reaction is limited to examples with two olefins with clearly different hydroformylation rates. If, however, a preformed aldehyde is added to the reaction mixture, various types of unsymmetrical tertiary amines are obtainable. The primary amine performs reductive amination with the aldehyde to give a secondary amine undergoing hydroaminomethylation with the olefin in a final step. By use of ketones instead of aldehydes the synthetic potential can be broadened (eq 84).[174]



(eq. 84)

entry	carbonyl compound	amine	yield [%]
1	isobutyraldehyde	*n*-butylamine	91
2	isobutyraldehyde	aniline	74
3	benzaldehyde	benzylamine	94
4	acetone	*n*-butylamine	82
5	benzylmethylketone	benzylamine	92

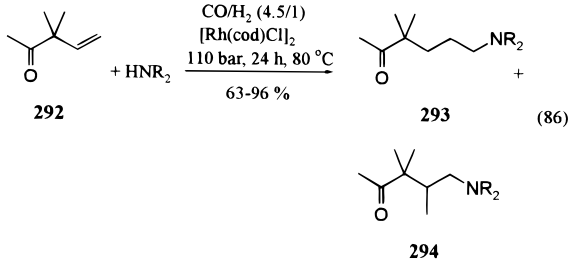
This procedure can also be applied to intramolecular cyclizations yielding N-heterocycles such as **291**, if substrates of type **290** with carbonyl and olefin functionality are used (eq 85).[174]



(85)

$R^1 = CH_3$; $R^2 = CH_3$ 31 %
$R^1 = R$-(+)-CH_3; $R^2 = Ph$ 85 %

In the presence of secondary amines the ketone group remains unaffected. Thus the hydroaminomethylation of **292** leads to tertiary amines **293** and **294** in good up to excellent yields (eq 86). The

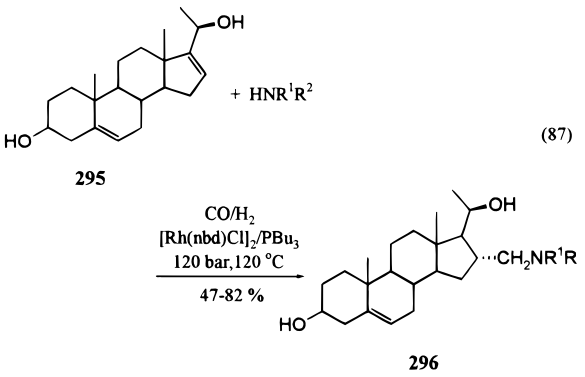


(86)

aminohexanones of type **293** obtainable according to

this procedure exhibit a structural pattern found in methadone analogues.[166] Under modified conditions, however, the unsaturated ketone **292** gives cyclic amines similar to **291.**[216]

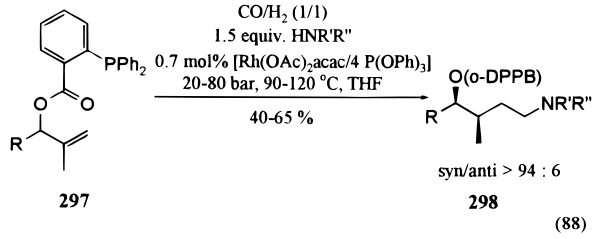
Hydroaminomethylation of the steroid allylic alcohol **295** with various secondary amines due to the allylic alcohol functionality proceeds diastereoselectively in moderate up to good yields to the corresponding aminomethyl steroid **296** (eq 87).[198]



(87)

HNR^1R^2 = diethylamine, piperidine, pyrrolidine, morpholine, N-methylpiperazine, N-formylpiperazine

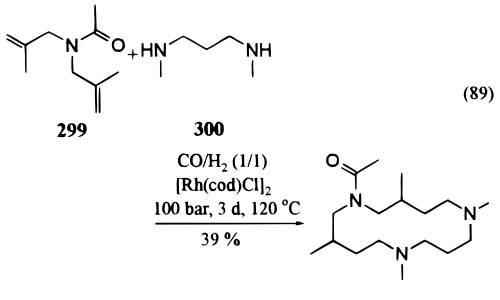
Similarly *o*-DPPB-functionalized methallylic alcohols **297** undergo diastereoselective hydroaminomethylation (>88% de) leading to the corresponding secondary or tertiary amines **298** in good yields (eq 88). This diastereoselectivity is induced by a precoordinating effect of the stereodirecting phosphine group in the *o*-DPPB moiety.[199]



(88)

o-DPPB = *ortho*-diphenylphosphorylbenzoate

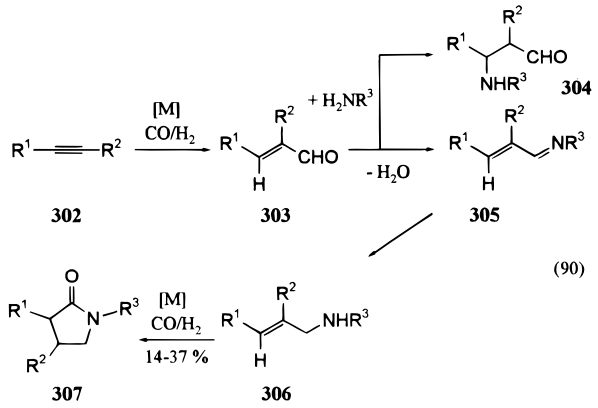
The intermolecular hydroaminomethylation can be extended to the synthesis of polyazamacrocycles, if α,ω-diolefins and secondary α,ω-diamines or primary amines are used as starting materials. Compared to common strategies this methodology offers a very efficient synthetic route to substituted macrocyclic polyamines with high variability. For example diolefin **299** in the presence of diamine **300** undergoes ring closure to form the macrocyclic triaza-system **301** with notable yields (eq 89).[200]



(89)

f. Hydroaminomethylation of Alkynes

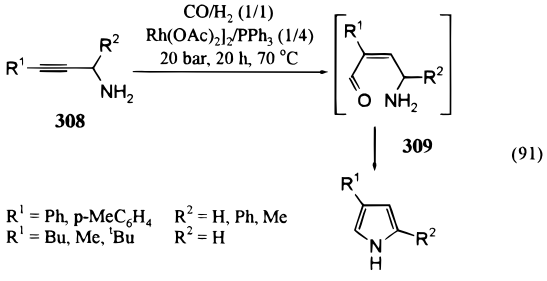
Similar to alkenes, alkynes also may serve as unsaturated compounds in hydroaminomethylation reaction sequences. Although synthetically attractive, only few investigations toward hydroformylation of alkynes in the presence of N-nucleophiles are known. Usually a preferred transformation to furanonic derivatives is observed under hydroformylation conditions.[201−205] In principle an α,β-unsaturated aldehyde **303** generated under hydroformylation conditions may undergo various subsequent reactions in the presence of amines. On one hand, nucleophiles can react in a Michael type 1,4-addition to form the aminoaldehyde **304**.[157] On the other hand the aldehyde **303** can undergo condensation with a primary amine to give an unsaturated imine **305** (eq 90). After



(90)

hydrogenation an allylic amine **306** can undergo the reactions as mentioned above. In this way various lactams of type **307** can be obtained in moderate yields.[196] Major byproducts in this multistep sequence are the corresponding furanone and mono- or bisamides resulting from an insertion of the amine into the metal−acyl species during the hydroformylation cycle.

Intramolecular versions of these rhodium-catalyzed reactions are more successful. Thus, aryl- and alkylpropargylamines **308** with syngas give 3-substituted or 2,4-disubstituted pyrroles **310** in good up to excellent yields. This one-pot synthesis includes hydroformylation of the alkyne to form unsaturated aldehydes of type **309** and intramolecular condensation with the amine group. Alkylpropargylamines lead to the corresponding pyrroles in lower yields compared with arylpropargylamines (eq 91).[206,207]



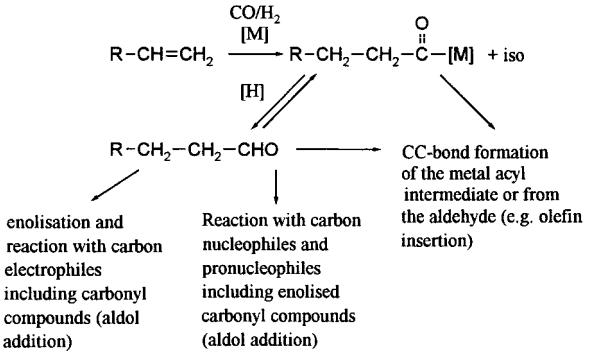
(91)

R^1 = Ph, p-MeC_6H_4 R^2 = H, Ph, Me
R^1 = Bu, Me, ^{t}Bu R^2 = H

V. Tandem Hydroformylations with Additional CC-Bond Formations

Under hydroformylation conditions numerous conversions with additional CC-bond formations can occur, either via reactions of the oxo aldehyde or its enolized carbon pronucleophiles as well as reactions of the metal acyl intermediate, e.g. through olefin insertion (see Scheme 6).

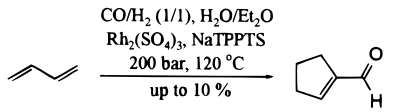
Scheme 6

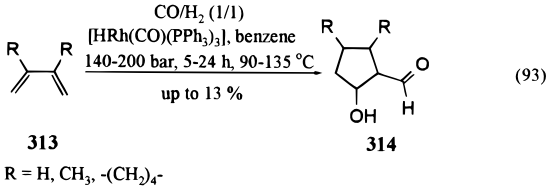


A. Hydroformylation/Aldol Reaction Sequences

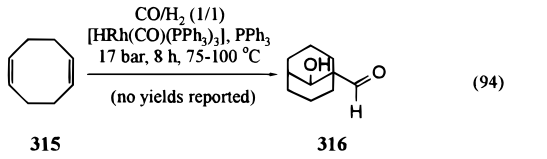
The aldol addition represents one of the most important reactions in synthetic organic chemistry.[208] Aldol reactions of oxo aldehydes are observed as side reactions under hydroformylation conditions.[1−9] Therefore some efforts have been made to combine hydroformylation with a consecutive aldol reaction in a one pot sequence. Here aldol addition of the enolized oxo aldehyde molecule to an oxo aldehyde can occur as a homo aldol addition or one of the two reaction partners present under hydroformylation conditions can undergo mixed aldol addition with the usual problems of selectivity.

Both intra- and intermolecular aldol reactions following hydroformylation are reported. Thus aldol reaction is observed in the hydroformylation of 1,3-butadienes **311** and **313** forming formylcyclopentenes **312** or 2-hydroxyformylcyclopentanones **314** in low yields (eqs 92 and 93).[209−212]

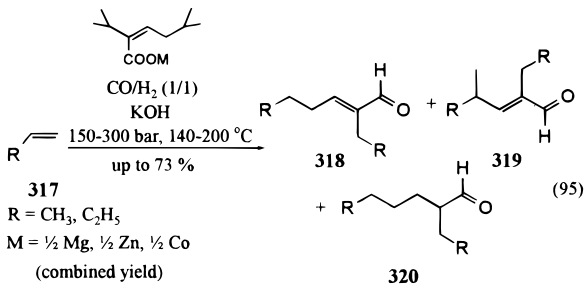




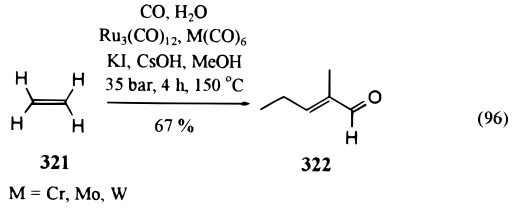
Similarly the hydroformylation of cyclic dienes (e.g. 1,5-cyclooctadiene **315**) in the presence of rhodium triphenylphosphine catalyst precursors leads to an intramolecular aldol addition of the intermediate dialdehydes in low yields (eq 94).[210−212]



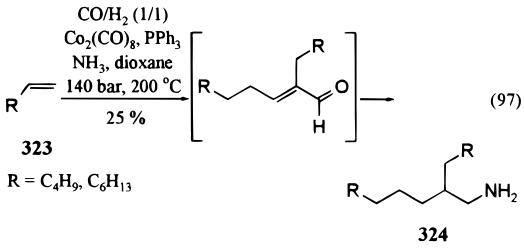
With monoolefins an intermolecular condensation proceeds after in situ generation of the oxo products forming α,β-unsaturated aldehydes. Good results are achieved if using a mixed-metal catalyst system of substituted metal acrylates and KOH (eq 95).[213]



Reaction of ethylene and carbon monoxide in the presence of $Ru_3(CO)_{12}$, $M(CO)_6$ (M = Cr, Mo, W), KI, CsOH, MeOH, and water gives 2-methylpent-2-enal (**322**) as the major product (eq 96).[214]

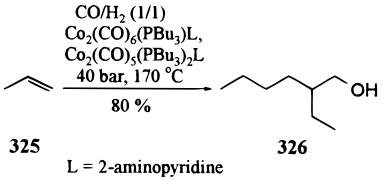


1-Hexene and 1-octene react in the presence of $Co_2(CO)_8$ and ammonia under hydroformylation conditions to aldol condensation products that undergo consecutive reductive amination leading to saturated, primary amines of type **324** (eq 97).[147]



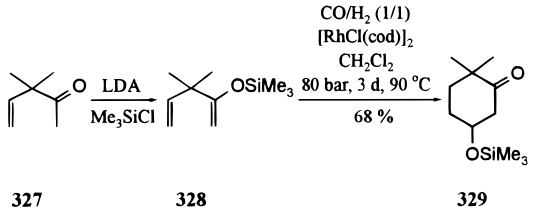
In an extension of the hydroformylation/aldol addition sequence higher alcohols are generated if starting from simple terminal olefins via hydroformylation, aldol condensation, and subsequent hydrogenation and reduction of the aldol condensation product. As promoters, zinc or magnesia oleates, stearates, or acetates can be added to the cobalt carbonyl catalysts to obtain the final products in good yields.[1−9] Thus using a mixture of $Co_2(CO)_6(PBu_3)L$ and $Co_2(CO)_5(PBu_3)_2L$ (L = 2-aminopyridine) the hydroformylation/aldol condensation sequence of propene leads to 2-ethylhexanol **326** (eq 98).[215]

Hydroformylation/aldol addition sequences can also be achieved if only one of the two components is generated via hydroformylation. This version is ap-



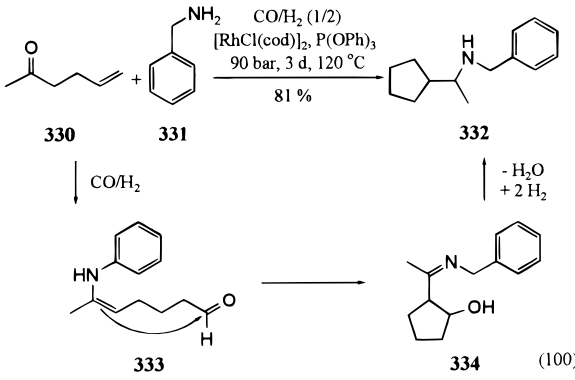
(98)

plied to unsaturated carbonyl compounds leading to carbocyclic ring products. The problems of chemo- and regioselectivity are circumvented by use of reactants with assigned reactivities. Thus the unsaturated silyl enol ether **328** undergoes selective hydroformylation at the unsubstituted double bond followed by a Mukaiyama type aldol addition (eq 99).[216] In this case the silyl enol ether moiety reacts as the C-nucleophile with complete transfer of the silyl function to the carbinol oxygen.



(99)

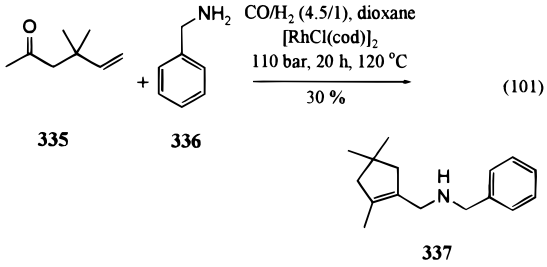
This reaction type proceeds even more conveniently if the C-nucleophile functionality is formed in situ under hydroformylation conditions. An approach in this direction includes the use of amines to build up imine/enamine structures that react via a Wittig type aldol condensation with the oxo aldehydes. Thus the γ,δ-unsaturated ketone **330** and benzylamine (**331**) under rhodium(I) catalysis with triphenyl phosphite as additive leads to the cyclopentane derivative **332** (eq 100).[217] A proposed mechanism starts with the



(100)

ketone function to undergo imine or enamine condensation, respectively, followed by hydroformylation leading to the linear aldehyde **333**. Intramolecular condensation leads to the cyclization product **334** which undergoes dehydration and a final hydrogenation and reduction to form the saturated amine **332**.

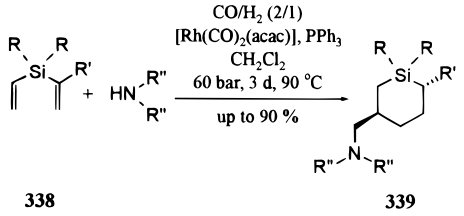
Conversion of the unsaturated ketone **335** under hydroformylation conditions in the presence of benzylamine (**336**) leads to the cyclopentene **337** (eq 101).[218] Due to steric hindrance, here, the enamine condensation predominantly takes place at the aldehyde moiety. As a consequence the ketone function serves as the acceptor leading to a cyclopentene with different chemoselectivity compared to the example



(101)

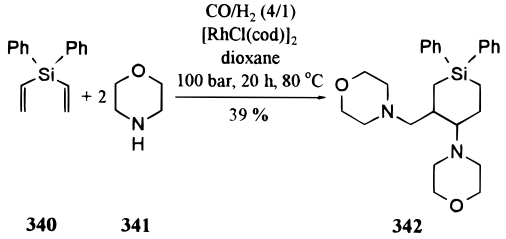
above. The final hydrogenation of the *endo* double bond to the saturated cyclopentane derivative is here prevented by the high degree of substitution.

Divinylsilanes of type **338** under hydroformylation conditions in the presence of secondary amines give silacyclohexane derivatives of type **339**. In this reaction 2 equiv of carbon monoxide is incorporated, and in analogy to the mechanism shown in eq 100, an aldol reaction leads to the cyclization forming six-membered rings. After elimination and hydrogenation steps the silacycles **339** are formed (eq 102).[219] The reaction proceeds with high stereoselectivity.



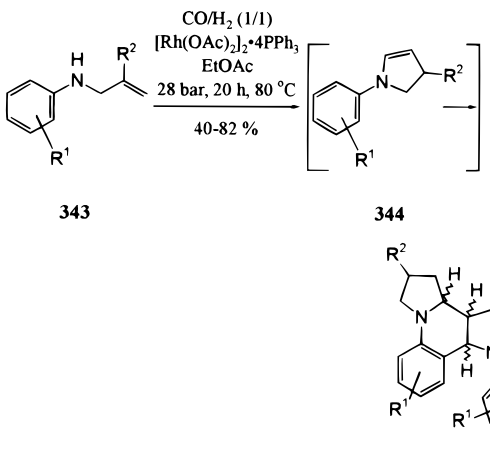
(102)

With variation of the hydroformylation conditions the same substrates are converted via an alternative pathway. With incorporation of 2 equiv of morpholine the silaheterocyclic diamine **342** is formed (eq 103).[219]



(103)

Obviously the formation of **342** occurs via formation and condensation of an enamine and an imine moiety, whereas in the former example (eq 102)



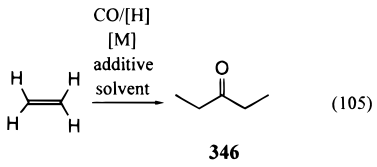
(104)

cyclization to the monosubstituted rings **339** may result after addition of an aldehyde and an enamine function as C-nucleophile. An analogous self-condensation of enamine/imine functionalities is observed with allylic arylamines **343** (eq 104).[220] Final intermolecular electrophilic aromatic substitution of the resulting iminium species completes the sequence to form the polycyclic system **345**.

B. Hydrocarbonylation/Insertion Sequences Leading to Ketones

a. Hydrocarbonylation of Ethylene

Under hydroformylation conditions occasionally the formation of ketones is observed.[1−9] This reaction type (hydrocarbonylation) has been optimized toward ketone formation in several cases. Thus starting from ethylene, diethyl ketone (**346**) formation is a well-established process (eq 105).[221−237]



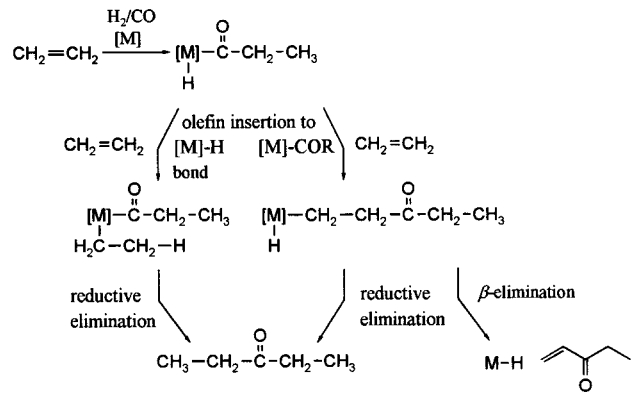
(105)

346

[M]: e. g. $Co_2(CO)_8$, Rh_2O_3, $Rh(H)(CO)(PPh_3)_3$

Mechanistically the initial steps of the reaction pathway follow the classical hydroformylation mechanism of Heck and Breslow.[222−224] The olefin undergoes hydrometalation and carbon monoxide insertion to form the metal acyl complex. If, instead of hydrogenolysis, a second olefin insertion takes place followed by a terminating reductive elimination, saturated ketones are formed. Formation of unsaturated ketones via β-H elimination can also occur (Scheme 7).

Scheme 7



Numerous metal complexes have been investigated as catalyst precursors for this type of ketone formation.[221−237] The efficiency of ruthenium catalyst precursors in combination with various bases as well as the influence of pressure, carbon monoxide-to-ethylene ratio, temperature, and water content of the solvent is examined.[225] It is observed that ruthenium catalysts and base promoters prove to be efficient systems for the synthesis of diethyl ketone (**346**) from ethylene and CO in the presence of 2-propanol or 2-butanol under mild conditions.[225] Ruthenium−iodide systems are found to catalyze the reaction of olefins, carbon monoxide, and alcohols to give ketones and esters. Using the system $Ru_3(CO)_{12}$ and phenyl iodide at elevated temperatures (190 °C), the yield of diethyl ketone (**346**) is optimized to 47%.[226]

Use of $Ru_3(CO)_{12}$ and tricyclohexylphosphine as catalytic system in the hydrocarbonylation reaction of ethylene leads to diethyl ketone formation in only minor yields. It is, however, remarkable that this reaction proceeds in the absence of CO and H_2 since methyl formate serves as the source of syngas via CH activation.[227]

The tetrarhodium dodecacarbonyl system catalyzes the reaction of ethylene via water gas shift equilibria with water as the hydrogen source and formation of oligomeric ketones. Addition of triethylamine changes the feature of the reaction giving diethyl ketone (**346**) in good yields.[228]

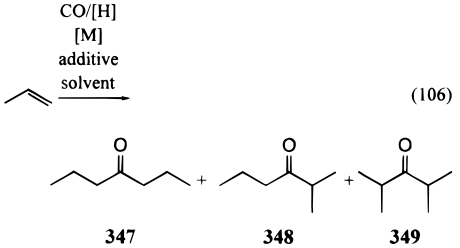
The reaction of ethylene and syngas at 1 atm in the presence of Pd(II)/PPh_3 catalysts proceeds with selectivities up to 99%. It is reported that the rate and selectivity of the ketone formation (relative to the sum of the ketones and acids formed) depend on the chosen solvent, aqueous CF_3COOH. The most important parameter is the concentration of water in CF_3COOH.[229]

High selectivities in the dicobalt octacarbonyl catalyzed hydrocarbonylation of ethylene are reported using phosphines, e.g. DPPE in a dioxane water mixture. The selectivity and activity is examined as a function of the ethylene and the H_2O concentration as well as of the CO pressure. The selectivity of diethyl ketone is fairly high under the variety of the conditions studied.[230,237]

Diethyl ketone formation is also investigated with use of various supported transition metal catalysts. Best results are achieved with rhodium supported on active carbon. In this case the rate of ketone formation is higher than the aldehyde generation.[231−234] Furthermore, sulfided rhodium, iridium, and Ni/Mo carbon-supported catalysts are used under hydroformylation conditions generating diethyl ketone from ethylene. The less expensive Ni/Mo catalysts show higher selectivity than rhodium or iridium catalysts. The reaction can be carried out in a fixed bed flow reactor at about 300 °C using a mixture of CO, H_2, N_2, and small amounts of H_2S.[235,236]

b. Hydrocarbonylation of Propene

The hydrocarbonylation of propene usually proceeds with lower yields if compared with ethylene.[21,237−240] Furthermore, three different regioisomers **347**−**349** of dipropyl ketones are observed due to *n*,iso-hydrometalation and head−tail insertion of the olefin into the metal acyl species (eq 106).



(106)

347 **348** **349**

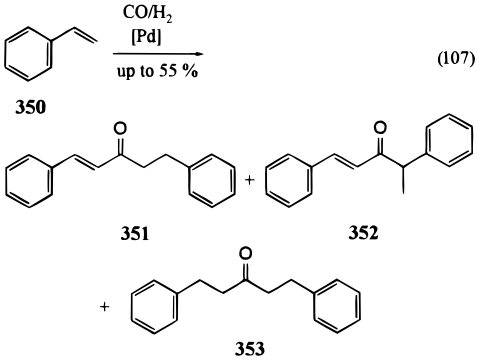
[M]: e. g. $Rh(acac)_3$, Raney-Co

Isomeric dipropyl ketones **347**−**349** are generated from propene under water gas shift conditions. Using several $Co_2(CO)_8$−phosphine systems, reaction parameters were investigated; however, even under best conditions, only minor yields are obtained with a mixture of all isomers.[237]

More recently some efforts have been made to apply heterogeneous catalysis to the hydrocarbonylation reactions.[21] The hydrocarbonylation of propene leading to ketones with rhodium-exchanged zeolites is reported to proceed with low yields. 2,4-Dimethyl-3-pentanone (**349**), 2-methyl-3-hexanone (**348**), and 4-heptanone (**347**) are formed in less than 5% of the butyraldehyde production.[238,239] Good results, however, show palladium trimethylphosphine carbonyl clusters encaged in zeolite NaY with a remarkable selectivity in the hydrocarbonylation of propene. The major products are propane and C_7-ketones, especially 2-methyl-3-hexanone (**348**), while C_4-aldehydes are only minor products. The formation of C_7-ketones as minor side products is attributed to an addition of C_4-aldehyde to the double bond of propene (hydroacylation).[240]

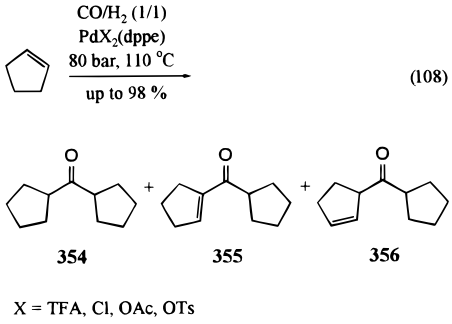
c. Hydrocarbonylation of Styrenes and Other Olefins

The reaction of styrene (**350**) under hydroformylation conditions leads to saturated and α,β-unsaturated ketones.[241,242] The latter are generated by a final β-H elimination step forming a highly conjugated enone system, which is less easily hydrogenated (eq 107).



The $[Pd(CH_3CN)_4](BF_4)_2$ complex modified with various phosphine, nitrogen, and mono- or bidentate phosphorus ligands catalyzes the formation of *E*-1,5-diphenylpent-1-en-3-one (**351**) in selectivities up to 80%. The hybrid ligands used, particularly phosphine thioethers, switch the regioselectivity to bring about a largely selective formation of **352**. The saturated product **353** is formed only in minor yields.[241,242] Considerable amounts of the linear ketones **351** and **353** are obtained in good yields if using Pd(dppp)-$(p\text{-}MeC_6H_4SO_3)_2$ as the catalyst precursor.[243] In addition, use of the complexes $[Pd(CH_3CN)_2(dppp)](BF_4)_2$ and $[Pd(OTf)\{(CH_3)_2CO\}(dppp)](OTf)$ gives high ketone products selectivity.[241] This method has been applied to other styrene derivatives e.g. *o*-methylstyrene.[244]

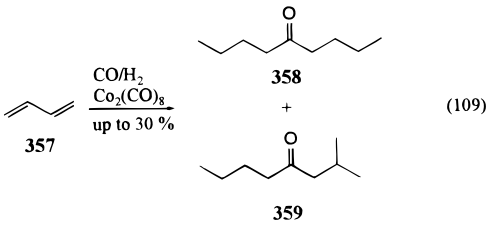
Hydrocarbonylation of cyclopentene with PdX_2-(dppe) (X = TFA, Cl, OAc, OTs) catalyst precursors to form saturated and unsaturated ketones **354**−**356** is influenced by hydrogen bonding of urea derivatives to the anionic ligands X of the catalyst precursor (eq 108).[245]



Formation of ketones starting from various olefins is carried out using equimolar amounts of $Ph(Et)_2N$:BH_3 complex and anhydrous $CoCl_2$ in the presence of CO at room temperature to give the dialkyl ketones in moderate to good yields after oxidation with H_2O_2.[246] The reaction may proceed starting with hydroboration followed by boron/CO exchange induced by a cobalt carbonyl species that is generated from $CoCl_2$ via cobalt hydride species.

d. Hydrocarbonylation of Conjugated Dienes

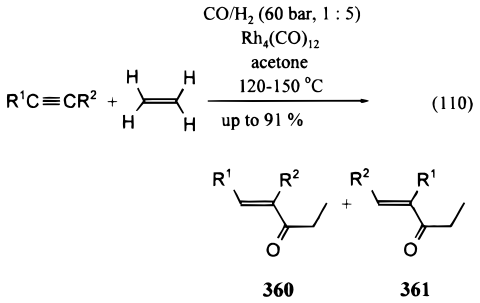
Some investigations have been made on the reaction of butadiene (**357**) under hydroformylation conditions. Normally, the reaction proceeds with low selectivity.[210] Only in a few cases a considerable amount of dibutyl ketones **358** and **359** is observed (eq 109).



Reaction of 1,3-butadiene (**357**) and syngas in the presence of catalytic amounts of dicobalt octacarbonyl yields C_9-ketones **358** and **359** in up to 30%. The majority of the dienes is converted to saturated monoaldehydes and to polyketones.[247,248]

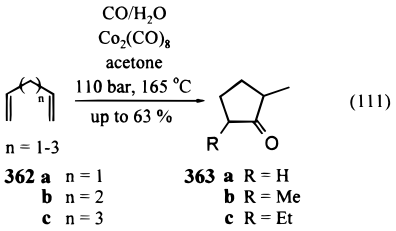
e. Mixed Hydrocarbonylation of Acetylenes and Ethylene

Hydrocarbonylative coupling of two alkyne units to form dienones has not been reported. Rhodium carbonyl catalyzed mixed hydrocarbonylation of acetylenes and ethylene with carbon monoxide and hydrogen leads to α,β-unsaturated ethyl ketones **360** and **361** in very good yields.[249,250] The reaction pathway is initialized by *cis*-hydrometalation of the acetylene. Here the rhodium moiety is added to the sterically less hindered side of the alkyne with high stereo- and regioselectivity (eq 110).[249,250]



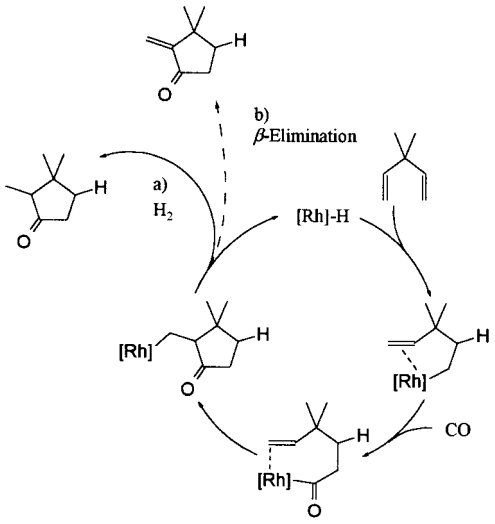
f. Hydrocarbonylative Cyclization of Nonconjugated Dienes

In 1964 Klemchuk first described the formation of cyclopentanones from α,ω-dienes **362** under hydroformylation conditions.[251] Independent from the chain length between the two olefin units, cyclopentanones **363** are the preferred products. The conversion is carried out under cobalt catalysis and water gas shift conditions in a CO atmosphere (eq 111).[251−253]



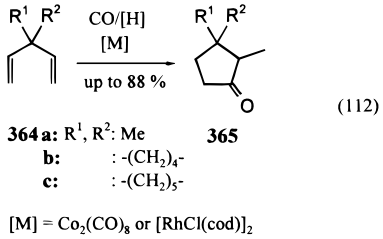
Mechanistic studies on the reaction of 1,4-dienes with the $HCo(CO)_4$ complex have been made by Heck[222−224] and Jonassen et al.[254] The reaction is proposed to be initiated by a hydrometalation of one of the two double bonds (Scheme 8).

Scheme 8



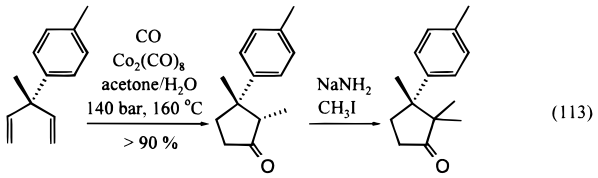
The metal alkyl complex then undergoes CO insertion to give a metal acyl complex. A further olefin insertion leads to the kinetically favored five-membered ring with a metal alkyl moiety at the exocyclic methyl group. Final hydrogenolysis or β-elimination liberates the product.

The reaction of 3,3-disubstituted 1,4-pentadienes **364** under similar conditions leads to monocyclic or spiroannulated cyclopentanones **365** with quaternary centers (eq 112).[130] Cobalt- and rhodium complexes

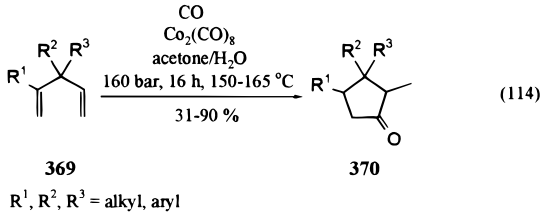


can be used as catalyst precursors. Hydrogen or water is used as hydrogen source. The quaternary center blocks isomerization and enhances the cyclization through a Thorpe−Ingold effect.[255]

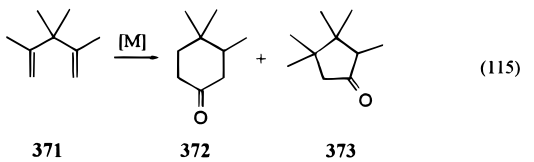
The hydrocarbonylative cyclization of 1,4-pentadiene **366** using $Co_2(CO)_8$ and CO under water gas shift conditions is applied in the synthesis of the aromatic sesquiterpene (±)-α-cuparenone **368** (eq 113).[256]



The ring-closing step of the synthesis is achieved in high yields giving a racemic mixture of two diastereoisomers of **367** in a 3:1 ratio (trans:cis). The thermodynamic equilibrium corresponds to a 20:1 ratio; thus, the product formation appears to be kinetically controlled.[257] Similar effects are observed at a series of other unsymmetrical 1,4-dienes **369** with quaternary centers at C-3. The result are assembled in Table 7 (eq 114).



Systems with substituents at the olefinic double bonds are less reactive. If the highly substituted diene **371** is converted, the generation of new quaternary centers via carbonylation is hindered (Keuleman's rule). With cobalt catalysts the carbonylation connecting the C1 and C5 atoms is preferred and leads to the cyclohexanone system **372** (eq 115).



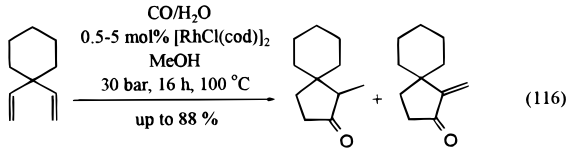
On the other hand, if using the rhodium complex $[RhCl(cod)]_2$ the kinetical favored cyclopentanone **373** is the sole cyclization product.[258] Further applications of this method are demonstrated with 1,4-dienes and 1,5-dienes bearing various substitution patterns to give substituted cyclopentanones in good yields.[259]

Table 7. Hydrocarbonylative Cyclization of Substituted 1,4-Pentadienes

entry	R^1	R^2	R^3	product **370** (%)	2,3-*trans*/*cis* ratio
1	H	Me	Ph	80	4:1
2	H	Ph	Ph	71	
3	H	Me	*p*-tolyl	90	4:1
4	H	Me	*m*-tolyl	87	4:1
5	Me	Me	Me	31	1:6[a]

[a] 2,4-trans/cis ratio.

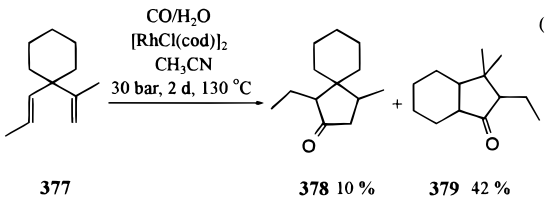
In addition rhodium catalyzed conversion of 1,1-divinylcycloalkanes, such as 1,1-divinylcyclohexane (**374**), under carbon monoxide pressure and water gas shift conditions leads to the spiroannulated bicycles **375** and **376** in up to excellent yields (eq 116).[258] The



(116)

product distribution can be controlled by variation of the catalyst and the concentration of the hydrogen source. A high catalyst/reactant ratio predominantly leads to the saturated ketone **375**, whereas a low ratio favors the formation of the exo methylene cyclopentanone **376**. In contrast to homogeneous rhodium catalysis with $[RhCl(cod)]_2$ the use of polymer attached CpRh(cod) complex provides the α,β-unsaturated cyclopentenones in higher yields.[260]

Under the reaction conditions of hydrocarbonylative cyclization of higher substituted 1,4-dienes, skeleton rearrangements are observed. If starting from diene **377** in competition to the normal reaction pathway to form the spiroannulated cyclopentanone **378** the hydroindenone system **379** is observed as a rearrangement product (eq 117).[131]

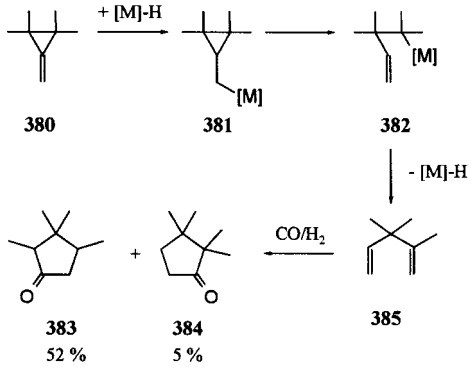


(117)

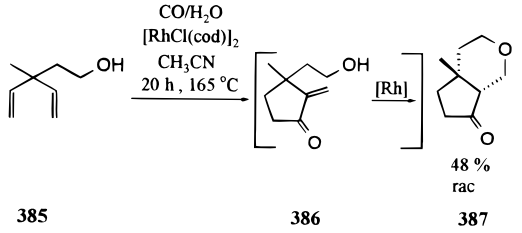
For this carbon skeleton rearrangement, metalated cyclopropyl carbinyl intermediates of type **381** are proposed. These can also be generated from methylenecyclopropanes, such as **380,** under hydroformylation conditions which react via a metal-mediated ring opening followed by hydrocarbonylation to form the cyclopentanones **383** and **384** in a 10:1 ratio (Scheme 9).[131]

A variety of functional groups in the C3-side chain of 3,3-disubstituted 1,4-pentadienes is tolerable under the reaction conditions of rhodium or cobalt catalyzed hydrocarbonylative cyclization.[261,262] Dienes with ester, alkoxy, and acetate groups lead to the corresponding cyclopentanones in medium to good yields. Free carboxylic acid and aldehyde functions are not tolerable and suppress the formation of cyclization products. Surprisingly the alcohol **385**

Scheme 9

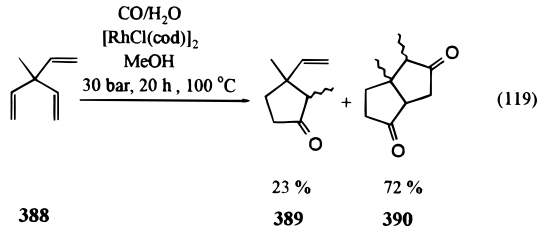


yields the annulated pyrane system **387**. The formation of this product is interpreted to stem from rhodium-catalyzed intramolecular conjugate addition to the enone unit of exo methylene cyclopentanone **386** as an intermediate (eq 118).[261]



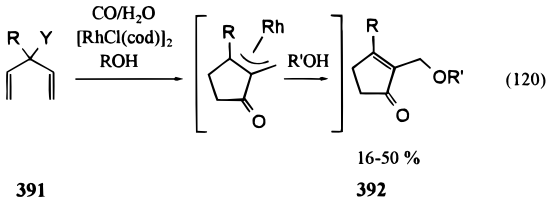
(118)

The reaction of 3-methyl-3-vinyl-1,4-pentadiene (**388**) gives only small amounts of the normal cyclization product **389** whereas the bicyclic diketone **390** is formed in good yields via a double hydrocarbonylative cyclization mechanism (eq 119).[262]



(119)

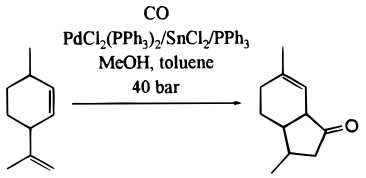
1,4-Dienes of type **391** with a leaving group in the C-3 position react under typical hydrocarbonylative cyclization conditions to cyclopentenones of type **392** (eq 120).[263] It is observed that the solvent used is incorporated, and a nucleophilic attack on a metal allyl complex intermediate is suggested.



(120)

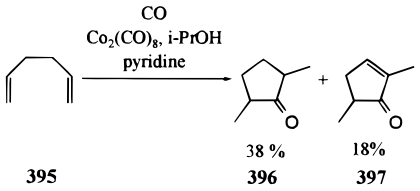
The system $PdCl_2(PPh_3)_2/SnCl_2/PPh_3$ proved to be an efficient catalyst precursor for the hydrocarbonylative cyclization of terpenoid 1,4-dienes such as

trans-isolimonene (**393**) to form the unsaturated hydroindanone derivative **394** as a mixture of diastereoisomers (eq 121).[264,265] The double bond generated results from a β-H elimination of the alkylmetal intermediate in the final step.



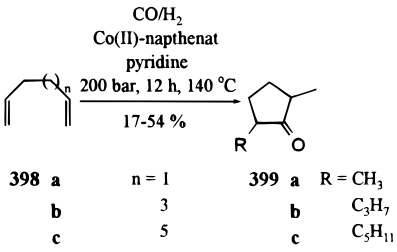
(121)

The reaction of 1,5-hexadiene (**395**) was carried out with catalytical amounts of various cobalt compounds, tertiary aromatic amines, and secondary alcohols as hydrogen source and solvents. These reactions lead to a 2:1 mixture of the saturated and unsaturated cyclopentanone derivatives **396** and **397** (eq 122).[266] Generation of unsatured products has been prevented by using CO/H_2 mixtures and a Co(II)−naphthenate/pyridine system.[267]



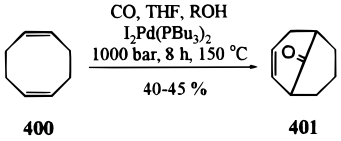
(122)

The formation of five-membered ring systems is strongly preferred. Even if higher homologues of 1,5-hexadienes **398**, e.g. 1,9-decadiene (**398c**), are treated under similar reaction conditions, double bond isomerization occurs and the corresponding 2-methyl-5-alkyl-cyclopentanones **399** are formed (eq 123).[267] Cyclic ketones of this type are of some interest as synthetic building blocks or components in fragrance industry.



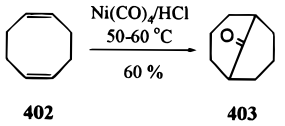
(123)

Using $I_2Pd(PBu_3)_2$ as catalyst precursor under drastic CO pressure, the reaction of 1,5-cyclooctadiene (**400**) leads to the bicyclic ketone **401** in moderate yields (eq 124).[268]



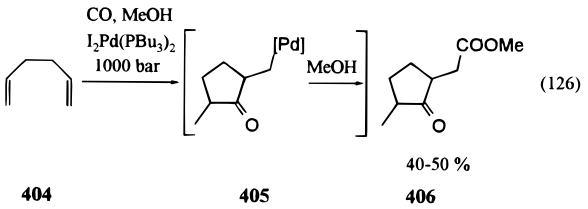
(124)

Similarly, stoichiometric reaction of 1,5-cyclooctadiene (**402**) with tetracarbonylnickel and aqueous HCl as hydrogen source leads to the formation of bicyclo[3.3.1]nonanone (**403**) in 60% yield (eq 125).[269]



(125)

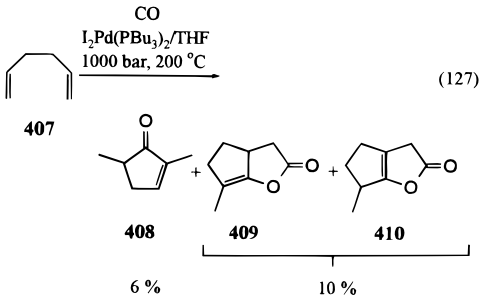
Hydrocarbonylative cyclization of 1,*n*-dienes with an additional consecutive hydrocarboxylation at the *exo*-methylene function was first described by Brewis and Hughes.[270] Best results were achieved with 1,5-hexadiene (**404**) and catalytical amounts of $I_2Pd(PBu_3)_2$ in methanol under drastic CO pressure (eq 126). The reaction follows the usual mechanism of



(126)

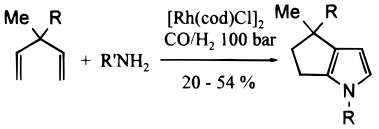
hydrocarbonylative cyclization (see above). The resulting alkyl−palladium bond in the intermediate **405** then undergoes CO insertion leading to an acylpalladium species, which is solvolyzed by the alcohol to form a γ-keto ester **406**.

Under similar reaction conditions using the aprotic solvent THF a similar reaction is observed. In minor yields the bicyclic enol lactones are isolated. Here after following the former mechanism, the palladium acyl intermediate reacts with the enol form of the ketone function (eq 127).[271]



(127)

Bicyclic lactone products are observed as side products of hydrocarbonylative cyclization of substituted 1,4-dienes.[257] In a similar conversion type various 1,4-dienes **411** in the presence of primary amines under hydroformylation conditions give bicyclic pyrroles of type **412.**[129] Here a 1,4-dicarbonyl intermediate reacts to form a pyrrole in the final step (eq 128).

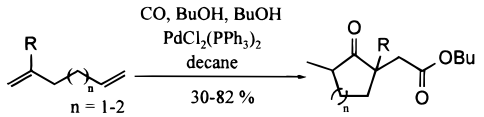


(128)

R = -Me, -CH(OH)CH_3, -CH_2CH_2OH

R' = i-Pr, Bu, Bn (*R*)-(+)-phenylethyl, *p*-methoxyphenyl

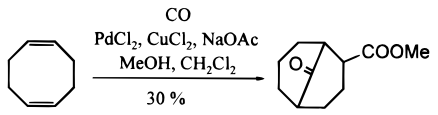
The $PdCl_2(PPh_3)_2$-catalyzed "cyclocarboxylation" of nonconjugated dienes **413** leads to the formation of γ-ketoesters **414** (eq 129). The resulting products suggest that the initial hydropalladation takes place at the less hindered olefinic bond.[272]



(129)

413 **414**

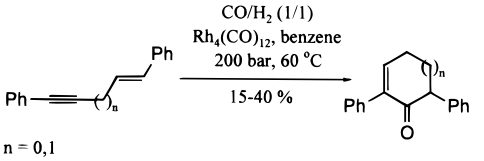
In a similar reaction sequence starting from 1,5-cyclooctadiene (**415**), if catalyzed by $PdCl_2/CuCl_2$/NaOAc in $MeOH/CH_2Cl_2$, the γ-ketoester **416** is formed (eq 130). It was found that the selectivity of the reaction is substantially influenced by the catalyst precursor and the cocatalyst.[273]



(130)

415 **416**

The hydrocarbonylative cyclization has also been carried out with enynes.[274,275] Using $Rh_4(CO)_{12}$ as catalyst precursor, α,ω-diaryl-substituted 1,3- and 1,4-enynes **417** react with syngas forming α,α'-diaryl-substituted cyclopentenones and cyclohexenones of type **418**, in moderate yields (eq 131).

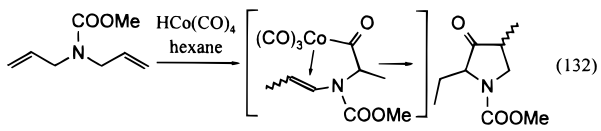


(131)

417 **418**

In this reaction, insertion of the alkyne triple bond into a rhodium hydrido species is assumed to be the initial step. The catalytic cycle then follows the typical mechanism of the hydrocarbonylative cyclization.

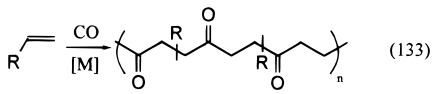
Cyclocarbonylation is also observed with bisallyl carbamate **419** reacting with $HCo(CO)_4$ to form the ketone **421**. A cobalt acyl olefin complex **420** has been postulated to be an intermediate which then undergoes a consecutive conversion to the five-membered cyclic ketone **421** (eq 132).[276]



(132)

419 **420** **421**

In analogy to the ketone formations described above the copolymerization of alkenes and carbon monoxide leads to the corresponding polyketones (eq 133). The mechanism of the copolymerization proceeds similar to those of the ketone formations. Here too as a starting sequence, an insertion of an alkene



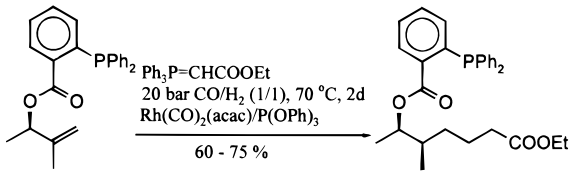
(133)

polyketone

into a metal hydride species with a subsequent carbon monoxide incorporation leading to the acyl-metal complex is discussed. Further insertion then leads to chain growing until termination occurs. The chain lengths can be controlled by varying the reaction conditions and the catalyst precursors. For detailed information, see refs[277,278] and the literature cited therein.

C. Miscellaneous Other Hydroformylations with Additional CC-Bond Formations

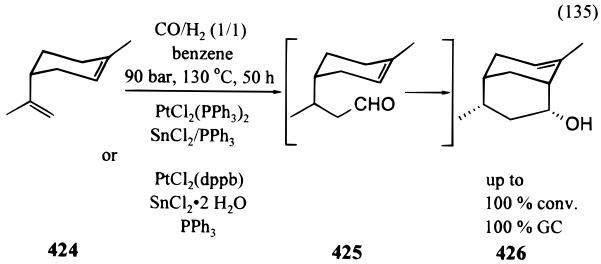
Various other hydroformylations with additional CC-bond formations are reported. Thus, hydroformylation in the presence of stable phosphorus ylids leads to a tandem Wittig procedure with olefin formation from the oxo aldehyde. This procedure with a consecutive hydrogenation of the resulting olefin was used in a diastereoselective hydroformylation/Wittig olefination/hydrogenation sequence starting from derivative **422** of a methallylic alcohol to give the saturated product **423** (eq 134).[279]



(134)

422 **423**

Hydroformylation can also be combined with a carbonyl ene reaction. This reaction sequence is observed in rare cases if nonconjugated olefins selectively are hydroformylated at one double bond and the resulting aldehyde can react with a remote double bond. Thus conversion of limonene **424** in a one-pot procedure forms two diastereoisomers of alcohol **426** using $PtCl_2(PPh_3)_2/SnCl_2/PPh_3$ or $PtCl_2$(diphosphine)/$SnCl_2/PPh_3$ systems (eq 135). Best results are achieved



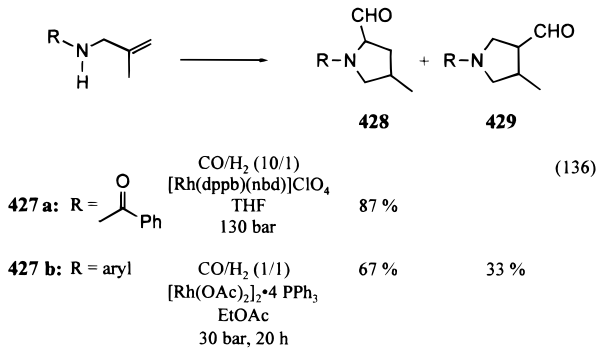
(135)

424 **425** **426**

with $PtCl_2$(dppb) complex. The mechanism of the final intramolecular cyclization step resembles an acid-catalyzed carbonyl ene reaction.[280] A similar example of a hydroformylation/ene reaction sequence is described above (eq 39).

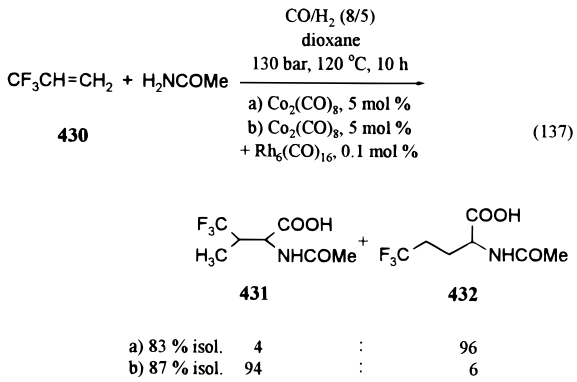
A reaction sequence starting from *N*-methallyl amides or *N*-methallylanilines **427**, respectively, is reported to proceed via hydroformylation of the

olefinic double bond and consecutive intramolecular enamine condensation, followed by a further hydroformylation of an enamine double bond and resulting in 2- and 3-formylpyrrolidines **428** and **429** (eq 136).[197,220,281]



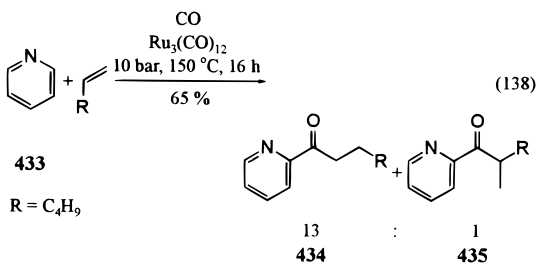
(136)

Following a similar mechanism in an intermolecular version the amino acid derivatives *N*-acetyltrifluorovaline (**431**) and *N*-acetyltrifluoronorvaline (**432**) are formed in high yields from 3-trifluoro-1-propene (**430**) in a dicobalt octacarbonyl catalyzed hydroformylation/amidocarboxylation sequence. The ratio of the regioisomers can be controlled from high amount of the straight chain product to high amounts of the branched product by addition of $Rh_6(CO)_{16}$ (eq 137).[282,283]



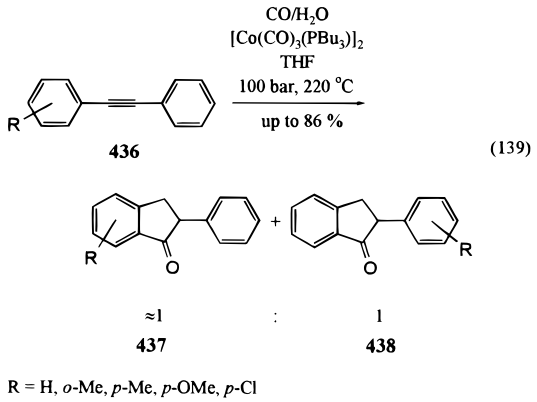
(137)

Hydroformylation can also be combined with CH-bond activation and ketone formation. Thus the reaction of olefins with CO under ruthenium carbonyl catalysis in pyridine leads to a mixture of pyridyl ketones **434** and **435** favoring the linear product. The ruthenium carbonyl cluster is expected to activate the *ortho*-CH bond of the heterocycle as the initial step of the reaction (eq 138).[284]



(138)

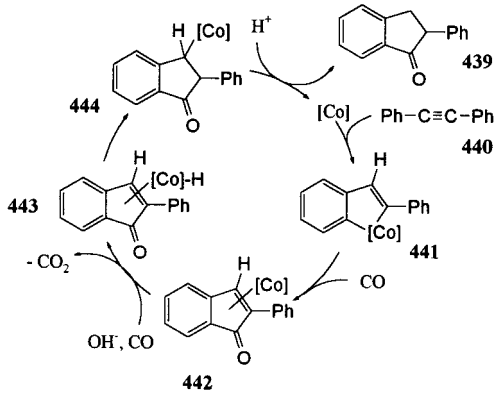
Similarly in an intramolecular version of this reaction type the hydroformylation of alkynes with cobalt complexes under water gas shift reaction conditions affords 2-substituted indan-1-ones **437** and **438** in satisfactory yields. Addition of phosphines enhances both the activity and the selectivity of the reaction. Various alkynes are converted to the corresponding indanones, but the regioselectivity at unsymmetrically substituted acetylenes is low (eq 139).[285,286] Similar reactions have been observed in intramolecular versions forming benzoanellated products from arenes with unsaturated side chains.[287,288]



(139)

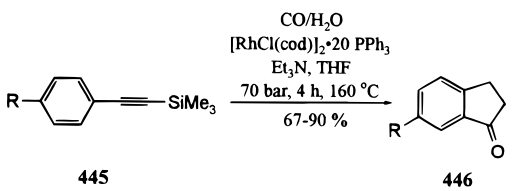
The reaction pathway leading to indan-1-one **437** (R = H) is outlined in Scheme 10.[285,286] Coordination

Scheme 10



of the alkyne **440** to a cobalt complex can induce an *ortho*-CH-bond activation and migration of the aromatic hydrogen to the acetylenic carbon to give cobaltaindene complex **441**. The formation of (indenone)cobalt complex **442** may proceed by replacement of the ring-bonded Co moiety in **441** by carbon monoxide. The resulting indenone product is then hydrogenated to yield the indanone **439** (Scheme 10).

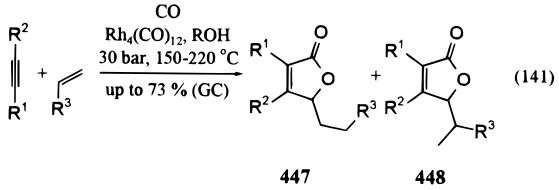
Under water gas shift reaction conditions, 1-aryl-2-(trimethylsilyl)acetylenes **445** undergo rhodium-catalyzed desilylative carbocyclization to form indanone **446**.[204] Both substituted phenyl as well as naphthyl groups are tolerated by the catalytical system. The reaction runs in good up to excellent yields (eq 140).[204]



(140)

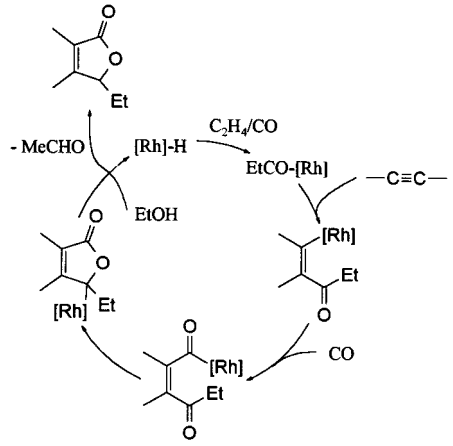
The mechanism proposed is comparable to that described in the scheme above. However, as the key step for the desilylation, an α-silyl carbonyl/silylenol ether rearrangement is proposed. A final hydrolysis liberates the indenone derivative.

Rhodium carbonyl complex catalyzed reactions of internal acetylenes with ethylene and CO in protic solvents as hydrogen source, e.g. ethanol, give 3,4-disubstituted 5-ethyl-2(5*H*)-furanones **447** and **448** in up to good yield (eq 141).[72]



The reaction is interpreted to start with ethylene and CO insertion into a hydrido rhodium species, followed by insertion of the acetylene derivative into the metal acyl unit. Further CO incorporation, ketone insertion, and a final hydrogenolysis complete the cyclization sequence (Scheme 11).

Scheme 11

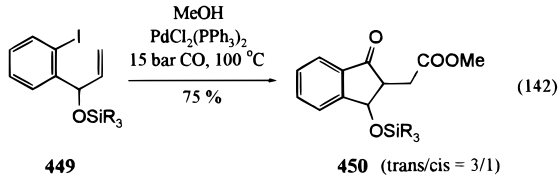


VI. Other Tandem Carbonylation Procedures Not Starting with Hydrocarbonylation

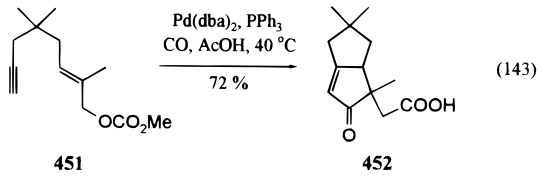
Tandem carbonylation procedures are not restricted to the hydroformylation and hydrocarbonylation/insertion sequences. Several other reactions initiating multistep carbonylation/insertion sequences are known. These, however, will not be covered in full detail in this article. Only some representative examples, leading to the relevant literature, are described.

Thus, Heck-type reactions starting with activation of a vinyl or aryl-C−halogen bond can be intercepted by olefin and carbon monoxide insertion sequences.[289,290] Reactions of this type are used in palladium-catalyzed cyclocarbonylation reactions. Thus the aryl iodide **449** is converted to the indanone **450** via a multistep insertion sequence (eq 142).[291]

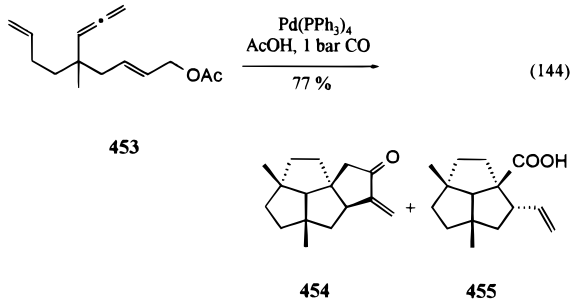
Various similar carbonylation reaction sequences starting with aryl halogen activation and different terminations are reported.[68,292−295] Another entry into palladium- and nickel-catalyzed carbonylation/insertion sequences is found with unsaturated allylic



acetates.[296−299] A typical example is the multistep cyclization of allylic carbonate **451** to form the bicyclic product **452**, an intermediate in the synthesis of (±)-hirsutene (eq 143).[298]

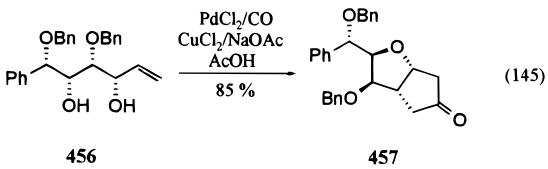


A more recent example is using allenes as additional reagents.[300] Tricyclic and tetracyclic products **454** and **455** are thus formed from alkenyl allenyl allylic acetate **453** (eq 144).



Similar reaction pathways are involved in inter- and intramolecular carbonylation/cyclization sequences starting from allylic halides and alkenes or alkynes.[289,301−303]

Another entry into carbonylation/insertion sequences is opened by an initial alkoxy- or amino-palladation step similar to the Wacker reaction however followed by insertion steps including carbonylation.[304−307] In a typical example this method was used in the synthesis of natural and unnatural enantiomers of gonio-furanone and its 7-epimers from D-glucose.[306] The key step is represented by the conversion of **456** to **457**.



VII. Concluding Remarks

In conclusion transition metal catalyzed carbonylation sequences represent a most powerful tool in the construction of new carbon skeletons. Hydroformylation and hydrocarbonylation of unsaturated compounds followed by C−O, C−N, and C−C bond-forming steps offer a convenient and versatile application of these reactions since they are starting from easily accessible materials. It can be expected

that more interesting examples and applications will come in the future.

VIII. Abbreviations

Ac	acetyl
acac	acetylacetonate
Ar	aryl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINAPHOS	(*R*)-2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl-(*S*)-1,1′-binaphthalene-2,2′-diyl phosphite
BIPHEPHOS	6,6′-{[3,3′-bis(1,1-dimethyl)-5,5′-dimethoxy-(1,1′-biphenyl)-2,2′-diyl]bis(oxy)} bis-(dibenzo[*d*,*f*][1,3,2]dioxaphosphepine)
Boc	*tert*-butyloxycarbonyl
BPPM	(2*S*,4*S*)-(−)-*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-(diphenylphosphino)methylpyrrolidine
Bu	butyl
Cbz	benzyloxycarbonyl
cod	1,5-cyclooctadiene
Cy	cyclohexyl
cp	cyclopentadienyl
dba	dibenzylideneacetone
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane
DMP	2,2-dimethoxypropane
DPPB	*ortho*-diphenylphosphorylbenzoate
DPPE	1,2-bis(diphenylphosphino)ethane
DPPH	1,6-(diphenylphosphino)hexane
DPPP	1,3-bis(diphenylphosphino)propane
Et	ethyl
Hal	halide
HMDS	hexamethyldisilazane
LDA	lithium diisopropylamide
Me	methyl
nbd	norbornadiene
NMe_2	dimethylamino
OTf	trifluoromethanesulfonate
$P(OPh)_3$	triphenyl phosphite
PCC	pyridine chlorochromate
PCy_3	tricyclohexylphosphane
PG	protecting group
Ph	phenyl
PPTS	pyridinium tosylate
Pr	propyl
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TPPTS	triphenylphosphine trisulfonate
Ts	tosyl

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CR970413R