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Synthetic Applications of Tandem Reaction Sequences Involving Hydroformylation

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Abstract Aldehydes obtained from olefins under hydroformylation conditions can be converted to more complex reaction products in one-pot reaction sequences. These involve heterofunctionalization of aldehydes to form acetals, aminals, imines and enamines, including reduction products of the latter in an overall hydroaminomethylation. Furthermore, numerous conversions of oxo aldehydes with additional *C*,*C*-bond formation are conceivable such as aldol reactions, allylations, carbonyl olefinations, ene reactions and electrophilic aromatic substitutions, including Fischer indole syntheses.

Keywords Aldol reactions · Fischer indole synthesis · Homogeneously catalyzed tandem reactions · Hydroaminomethylation · Hydroformylation

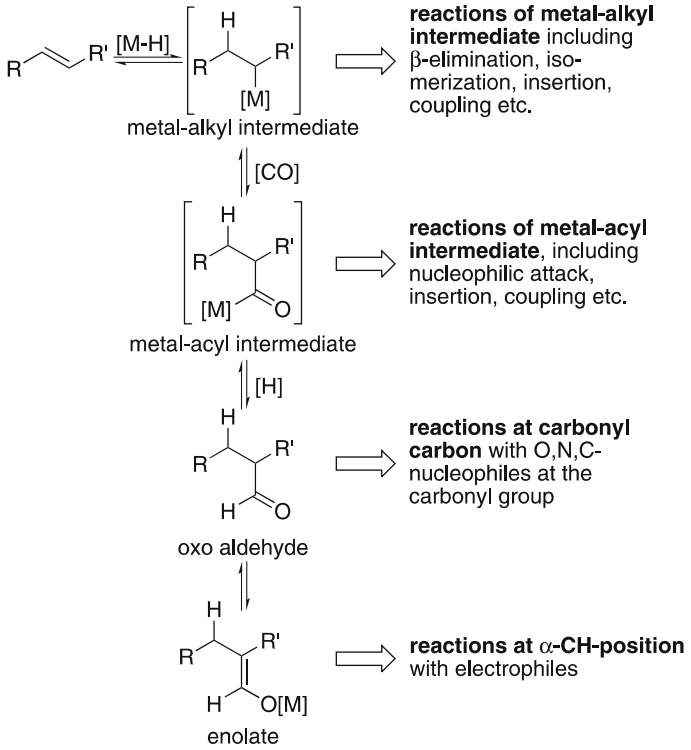
1 Introduction

The hydroformylation reaction ("oxo reaction") of alkenes with hydrogen and carbon monoxide is established as an important industrial tool for the production of aldehydes ("oxo aldehydes") and products derived there from [1–6]. This method also leads to synthetically useful aldehydes and more recently is widely applied in the synthesis of more complex target molecules [7–15, 17], including stereoselective and asymmetric syntheses [18–22].

Due to the versatile chemistry of the aldehyde group [23, 24], the products of hydroformylation are easily converted via reduction, oxidation, nucleophilic attack at the carbonyl group or electrophilic attack in the acidic α-position to give alcohols, amines, carboxylic acid derivatives, aldol condensation products and many others. Therefore, following the growing interest in the development of new and efficient non-catalyzed or homogeneously catalyzed one-pot reaction sequences [25], defined as "domino reactions", "reaction cascades" or "tandem reactions" [26], hydroformylation is a powerful synthetic method to be integrated in multi-step reaction sequences [27–29]. Tandem reactions, combining two or more different transformations in one synthetical procedure without change of reaction conditions and without addition of further reagents or catalysts require only one single setup of starting materials, reagents, and solvents and no isolation of intermediates is necessary. Therefore they save time and materials and furthermore they avoid waste of chemicals and solvents. At present, considerable effort is concentrated on the development of new procedures, even in total synthesis of more complex target molecules [30, 31].

Tandem procedures under hydroformylation conditions cannot only make use of the intrinsic reactivity of the aldehyde carbonyl group and its acidic α-position but they also include conversions of the metal alkyl and metal acyl systems which are intermediates in the catalytic cycle of hydroformylation. Metal alkyls can undergo β-elimination leading to olefin isomerization, or couplings, respectively, insertion of unsaturated units enlarging the carbon skeleton. Similarly, metal acyls can be trapped by addition of nucleophiles or undergo insertion of unsaturated units to form synthetically useful ketones (Scheme 1).

In this survey, selected synthetic applications of tandem hydroformylation sequences are described and complementing the more comprehensive reviews covering the literature up to 1998/99 [27], and up to 2003 [28, 29]. The material is ordered according to the type of the additional transformation involving heterofunctionalization of the aldehyde group to form acetals, aminals, imines and enamines, as well as reduction of the latter in an overall hydroaminomethylation. Furthermore, numerous conversions of oxo aldehydes with additional *C*,*C*-bond formation at the carbonyl group or at the acidic



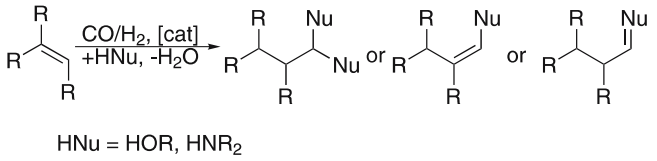
Scheme 1 Different stages of the hydroformylation and options for consecutive reactions

α-position are presented, such as aldol reactions, allylations, carbonyl olefinations, ene reactions and electrophilic aromatic substitutions, including Fischer indole syntheses. Not included here are the comprehensively described tandem reactions with isomerization of the double bond or reduction of aldehydes to alcohols and their further transformations as well as reactions involving conversions of the metals alkyl and metal acyl intermediates mentioned above.

2
Heterofunctionalization of Aldehydes Obtained via Hydroformylation

Hydroformylation in the presence of nucleophiles such as alcohols or amines leads to *O*,*O*- or *N*,*O*-acetals, aminals, imines or enamines (Scheme 2).

Imines and enamines under hydroformylation conditions can also be reduced to give saturated amines. With or without additional reduction, these conversions can be used in synthesis of various types of heterocycles.

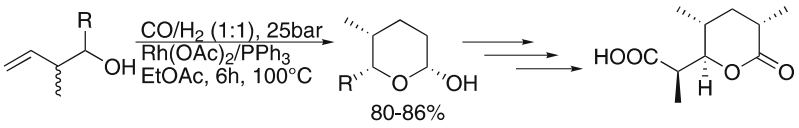


Scheme 2 Principle of hydroformylation in the presence of nucleophiles

2.1 Hydroformylation/Acetal Formation

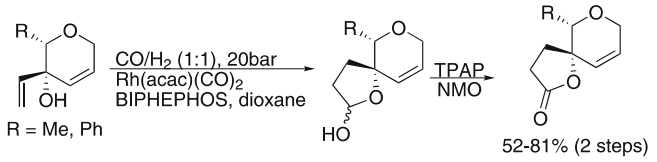
2.1.1 *O,O*-Acetal Formation

Acetalization of oxo aldehydes is used to protect sensitive aldehyde products, especially in asymmetric hydroformylation preventing racemization of an α-chiral aldehyde product [18–22, 27]. Acetal formation can also be applied to the synthesis of monocyclic or spirocyclic pyranes as potential precursors and building blocks for natural products such as pheromones or antibiotics. A representative example is the synthesis of the pyranone subunit of the Prelog–Djerassi lactone. For this purpose, various 1,2-disubstituted homoallylic alcohols were used (Scheme 3) [32].



Scheme 3 Formation of *O,O*-acetals under hydroformylation conditions

Di- or tetrahydropyrans with vinyl side chains obtainable by diastereoselective ring closing metathesis or by addition of vinylmagnesium chloride to appropriately functionalized tetrahydropyranones are converted to spirocyclic hemiacetals under hydroformylation conditions (Scheme 4) [33]. Oxidation yields the corresponding lactones.

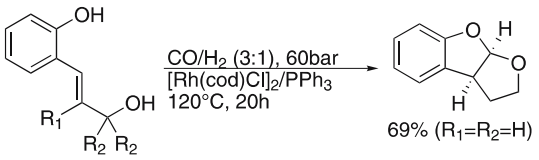


Scheme 4 Synthesis of spirocyclic γ-lactones

Similarly, δ-lactols and δ-lactones are obtainable from the corresponding homo allylic alcohols. With dehydration, the corresponding dihydropyrans are prepared. Spirocyclic γ-butyrolactones of this type and the corresponding δ-lactones are widespread in nature and play a key role as synthetic intermediates.

General Procedure for the Hydroformylation/*O,O*-acetal Formation. Synthesis of Spiro-*δ*-Lactones. A solution of the allylic alcohol (1 eq), $Rh(acac)(CO)_2$ (1.0 mol %), and BIPHEPHOS (4.0 mol %) in anhydrous dioxane was heated at 60 °C for 20 h under an atmosphere of carbon monoxide (10 bar) and hydrogen (10 bar) in an autoclave. The reaction mixture was filtered through basic alumina, and all organics were eluted with MTBE and then ethanol. The solvent was evaporated, and the crude hemiacetals were dissolved in DCM. Powdered molecular sieve (4 Å) and *N*-methyl morpholine-*N*-oxide (1.5 eq) were added, followed by TPAP (5 mol %). The mixture was stirred at ambient temperature until the starting material was completely converted as indicated by TLC (3 : 1 (v/v) hexane/EtOAc). The solvent was evaporated to one-third of the original volume, and the residue was filtered through a pad of silica. The products were eluted with MTBE and purified by flash chromatography, if necessary.

Similarly, furofuranes and benzofurofuranes known as substructure of aflatoxins are obtainable via hydroformylation of unsaturated diols. A representative example is given in Scheme 5 [34].

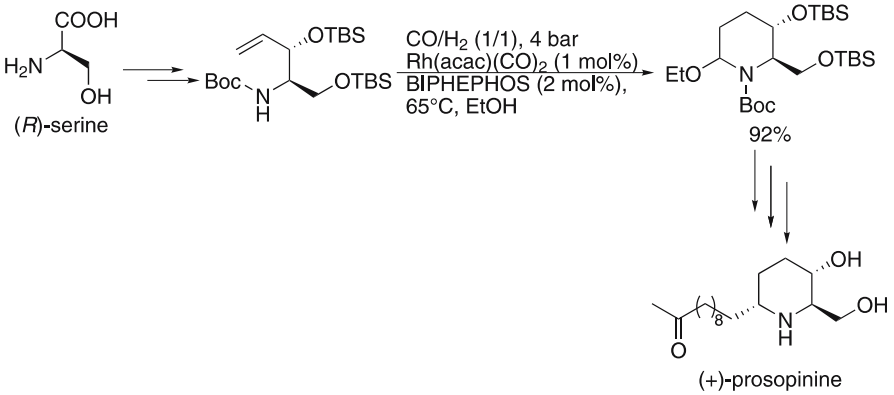


Scheme 5 Synthesis of aflatoxin analogous

2.1.2 *N,O*-Acetal Formation

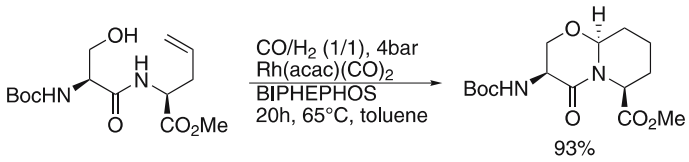
Hydroformylation of unsaturated amines offer a convenient synthetic access to cyclic *N*,*O*-hemiacetals. If performed in the presence of alcohols or orthoesters *N*,*O*-acetals are formed. With additional *N*-nucleophiles *N*,*N*-acetals are obtained. These compounds are synthetically attractive building blocks and were therefore used as a key step in the synthesis of various natural products [27, 35]. Thus the synthesis of (+)-prosopinine starting from enantiopure (*R*)-serine leads to a cyclic *N*,*O*-acetal functionality with the required functionality for the attachment of the side chain (Scheme 6) [36].

In addition, deoxoprosphylline [36], pipecolic acids, izidines [37], and the bicyclic alkaloids (±)-isoretronecanol, (±)-trachelanthamidine [38] and 6-epi-poranthellidine [39] were synthesized via tandem hydroformyla-



Scheme 6 Synthesis of (+)-prosopinine

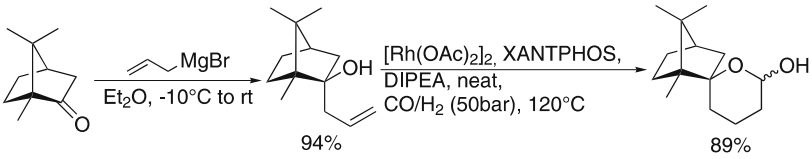
tion/cyclization. More recently, highly efficient syntheses of azabi-cyclo[4.4.0] alkane amino acids were achieved by Rh-catalyzed cyclohydrocarbonylation of dipeptides bearing a terminal olefin moiety and a heteroatom nucleophile [40]. Here the amine function as well as a second *O*-, *S*-, or *N*-Boc function are present in the acyclic starting material to form the bicyclic system with *N*,*O*-, *N*,*N*- or *N*,*S*-subunits in one step (Scheme 7).



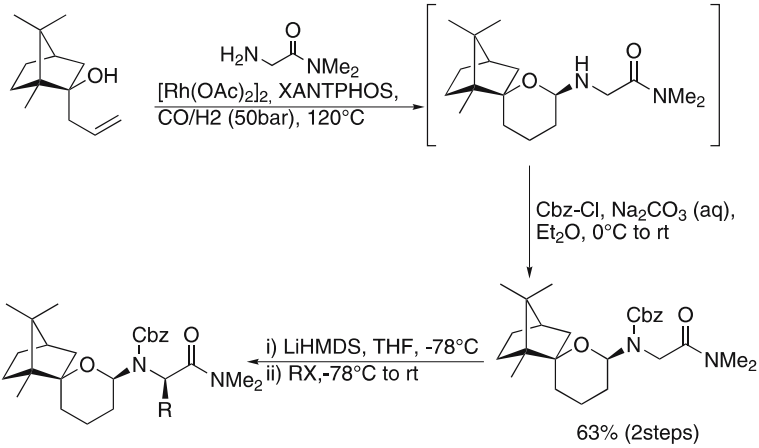
Scheme 7 Formation of *N*,*O*-acetals under hydroformylation conditions

Very recently the tandem hydroformylation/acetalization has been used for the synthesis of new synthetically valuable chiral auxiliary derived from camphor. Stereoselective allylation of camphor and subsequent terminal hydroformylation of the resulting homoallylic alcohol affords the δ-lactol auxiliary (camTHP*OH) in multigram scale (Scheme 8) [41].

If this hydroformylation is conducted in the presence *N*-nucleophile such as glycine dimethylamide the linkage of the substrate can be incorporated in the synthesis of the auxiliary. Subsequent Cbz protection affords a camTHP*-desymmetrized glycinamide building block that undergoes efficient and diastereoselective metal enolate alkylation. Acid mediated deprotection gives the *N*-Cbz protected α-amino amide products which may be converted directly to α-amino ketones on treatment with Grignard or organolithium reagents without loss of stereochemical integrity (Scheme 9) [41]



Scheme 8 Synthesis of camTHP*OH – a new chiral auxiliary

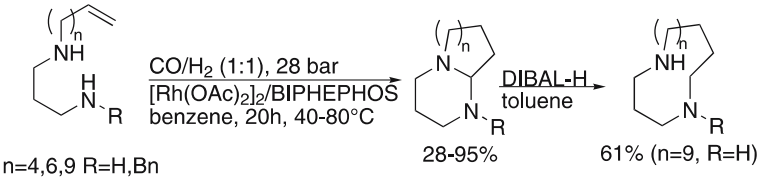


Scheme 9 Synthesis of desymmetrized glycinamide

General Procedure for the Hydroformylation/*N*,*O*-acetal Formation. Synthesis of camTHP*-desymmetrized Glycinamide. A stirred solution of the homoallylic alcohol (1 eq),$[Rh(OAc)_2]_2$ (0.1 mol % Rh), XANTPHOS (1 mol %), and glycinedimethyl amide (1.2 eq) under CO/H_2 (1 : 1, 50 bar) in a stainless-steel pressure vessel was heated to 120 °C for 16 h before being cooled to room temperature and depressurized to yield a yellow oil. The crude reaction mixture was diluted with Et_2O and saturated aqueous Na_2CO_3, cooled to 0 °C and stirred vigorously while benzyl chloroformate (1.5 eq) was added. The reaction was allowed to warm to ambient temperature and stirred under argon for 3 h before the addition of glycine (0.5 eq, to scavenge the excess benzylchloroformate) and the mixture stirred for a further 16 h. The biphasic mixture was diluted with water and extracted with EtOAc (3×). The combined organics were washed with brine, dried over $MgSO_4$, filtered through a pad of silica eluting with EtOAc and concentrated in vacuo to give a pale yellow oil. The crude product was purified by column chromatography (silica, petroleum ether (40–60 °C) : Et_2O, 9 : 1 gradient to neat Et_2O) to yield the title compound as a colorless oil (63%).

2.1.3
N,N-Acetal (Aminal-)Formation

N,*N*-Acetal formation used to prepare diazabicycloalkanes containing medium and large rings from *N*-alkenylpropane-1,3-diamines in excellent yields without the need for high dilution. Selective ring opening of these compounds leads to large heterocyclic rings (Scheme 10) [42–44].



Scheme 10 Formation of *N*,*N*-acetals under hydroformylation conditions

General Procedure for the Hydroformylation/*N*,*N*-acetal Formation. Synthesis of Biazacycloalkanes. The unsaturated diamine (1 eq), $[Rh(OAc)_2]_2$ (0.5 mol % Rh atoms) and BIPHEPHOS (2 mol %) were placed in an autoclave under N_2 followed by deoxygenated benzene The vessel was flushed and evacuated three times with CO/H_2 (1 : 1, 13 bar) and then pressurized to 28 bar. The reaction was kept at 40–80 °C for 20 h. The autoclave was cooled and the gases were released followed by selective extraction of the total product with light petroleum. Concentration of the solvent gave in most cases NMR pure material of the title compounds.

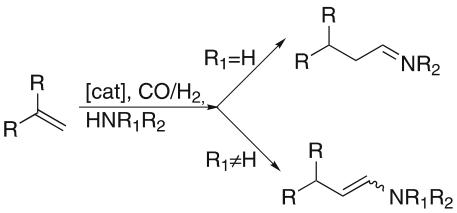
The same methodology can be applied to the synthesis of pharmaceutically relevant quinazolines and quinazolinones containing a fused alicyclic ring [45, 46].

2.2
Hydroformylation/Imine/Enamine Formation

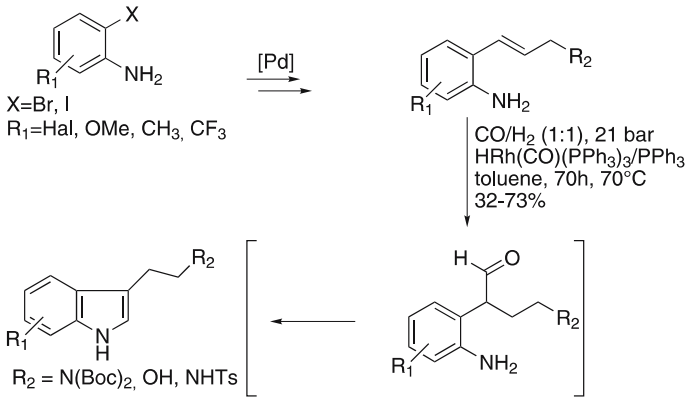
Similar to the formation of *N*,*N*-acetals under hydroformylation conditions attack of the carbonyl carbon by primary or secondary amines can lead to imines and enamines, respectively (Scheme 11).

In this manner, a hydroformylation/condensation sequence of *o*-vinylanilines give indoles directly. The starting *o*-vinylanilines are obtained by Heck reaction of the corresponding *o*-haloanilines. Hydroformylation of these styrene-type olefins proceeds preferably at the benzyl carbon. Intramolecular condensation gives pharmacologically interesting tryptophols and tryptamines in mediocre to good yields (Scheme 12, Table 1) [47].

General Procedure for the Hydroformylation/Enamine Formation. Synthesis of Indole Derivatives. A 300 ml autoclave equipped with a magnetic stirrer was charged with the



Scheme 11 Basic principle for imine and enamine formation under hydroformylation conditions



Scheme 12 Synthesis of indole derivatives from styrene-type anilines

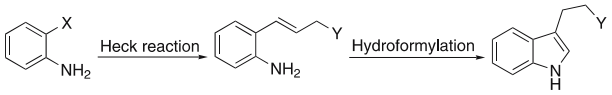
Heck adduct (1 eq), $HRh(CO)(PPh_3)_3$ (10 mol %), PPh_3 (50 mol %) and toluene. The autoclave was pressurized to 20 bar with 1 : 1 CO/H_2, and was heated at 70 °C for 72 h while stirring. The autoclave was cooled, cautiously vented, and the volatiles evaporated *in vacuo*. The resulting residue was chromatographed on silica gel eluting with hexane : EtOAc (4 : 1) to furnish the indole derivatives (for examples see Table 1).

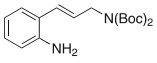
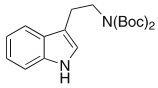
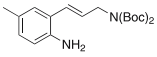
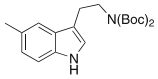
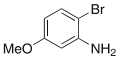
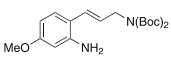
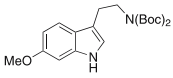
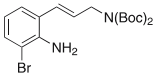
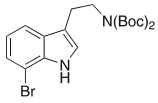
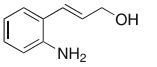
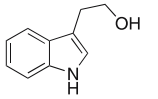
A similar formation of indoles has been achieved starting from *o*-nitrostyrenes. Under hydroformylation conditions, the nitro group is reduced to the amino group, which condenses with the in situ generated aldehyde [48].This approach is comparable with the indole syntheses of Reissert [49], Batcho and Leimgruber [50], and Sugasawa [51].

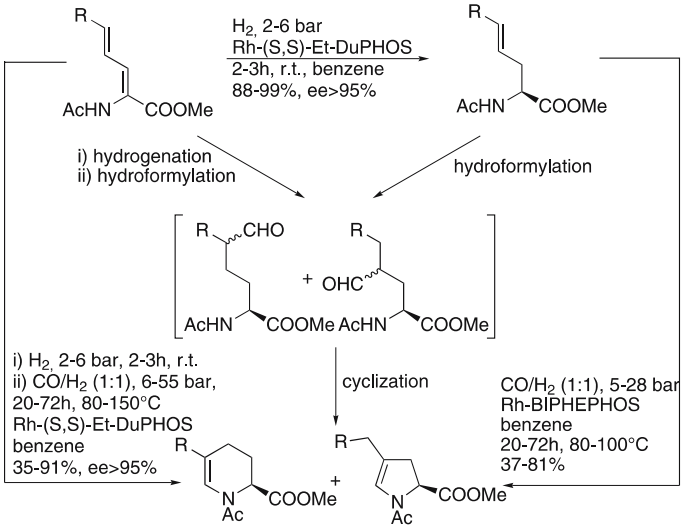
Cyclic α-amino acids with an enamine pattern can be obtained upon enantioselective hydrogenation followed by a hydroformylation/cyclization sequence in a single-pot version Rh(I)-DuPHOS acts as a catalyst for both steps, the enantioselective hydrogenation of prochiral dienamides and the hydroformylation of the resulting homoallylic amines (Scheme 13) [52, 53].

Very recently Jackson reported the use of supercritical carbon dioxide ($scCO_2$) in this tandem reaction, lowering the required total pressures of carbon monoxide and hydrogen [54].

Table 1 Examples for the synthesis of indole derivatives via hydroformylation of styrene-type anilines



		73%	 69%
		50%	 60%
		56%	 32%
		50%	 60%
		56%	 73%



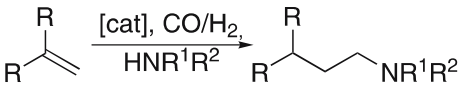
Scheme 13 Enantioselective Hydrogenation/hydroformylation/enamine formation

General Procedure for the Enantioselective Hydrogenation/Hydroformylation/Enamine Formation. Synthesis of Cyclic Enamine Amino Acids. Prochiral dieneamide (1 eq) and [(COD)Rh(I)-(*S*,*S*)-Et-DuPHOS] OTf (5 mol %) were dissolved in benzene and transferred

into an autoclave. The autoclave was charged with hydrogen (5 bar). After 3 h the hydrogen was vented and the autoclave was pressurized with CO/H_2 (1 : 1, 15 bar) and heated to 80 °C for 72 h. The autoclave was then cooled to ambient temperature and the solvent was removed under reduced pressure to give a yellow oil which is purified by column chromatography (silica, EtOAc : petroleum ether; 3 : 1).

2.3 Hydroformylation/Reductive Amination

Secondary and tertiary amines can be obtained if the hydroformylation of olefins is conducted in the presence of primary and secondary amines under elevated hydrogen partial pressures. Here the rhodium catalyst is involved in both steps, the hydroformylation of an olefin as well as the hydrogenation of the imine or enamine resulting from a condensation of the oxo-aldehyde with the amine (Scheme 14). This combination of hydroformylation and reductive amination is also known as hydroaminomethylation and has been applied to the synthesis of various substrates of pharmaceutical interest [55–57] as well as to the synthesis of macrocycles [60–63] and dendrimers [64, 65].

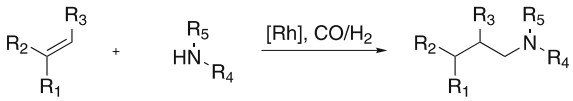


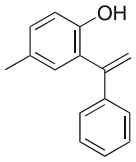
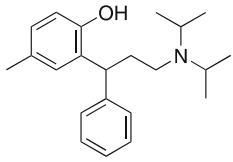
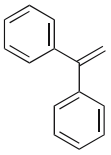
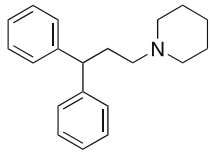
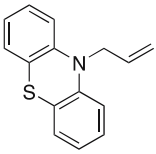
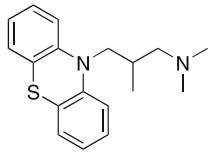
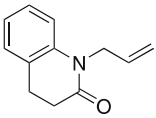
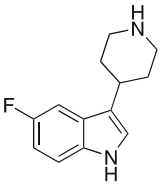
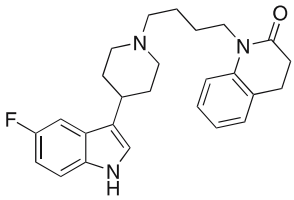
Scheme 14 Basic principle of the hydroformylation/reductive amination

For example, tolterodine, an important urological drug, has been prepared with good yields starting from 1-[2-hydroxy-5-methyl)phenyl]-1-phenylethylene via stepwise hydroformylation and reductive amination [58]. This synthesis can also be performed in a Rh/PBu_3 catalyzed one-pot tandem procedure starting from the diaryl ethene precursor giving 3,3-diarylpropylamine drugs in good yields [59]. If allylated phenothiazines are subjected to the hydroaminomethylation the antihistaminica alimemazine and etymemazine are obtained in good yields. Very recently the hydroaminomethylation has been used in the synthesis of dopamine-4-antagonists.

General Procedure for the Hydroformylation/Reductive Amination. Synthesis of 3,3-Diarylpropylamines. A mixture of the olefin (1 eq, 7.2 mmol), the corresponding primary or secondary amine (1 eq, 7.2 mmol) $[Rh(cod)Cl]_2$ (1 mol % Rh) and a defined amount of PBu_3 in anhydrous dioxane was heated for 3 d at 120 °C in a magnetically stirred autoclave under CO/H_2 atmosphere (9 : 2, 110 bar). The residue was dissolved in Et_2O and filtered through neutral alumina. Product mixtures were separated by column chromatography on neutral alumina using a mixture of MTBE/PE as eluent or by bulb-to-bulb distillation.

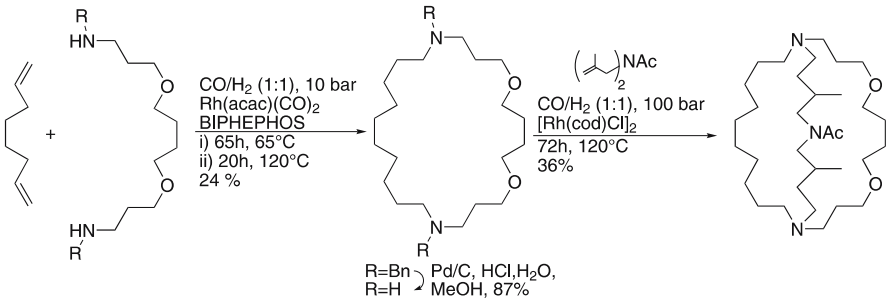
Table 2 Hydroaminomethylation in the synthesis of pharmaceuticals



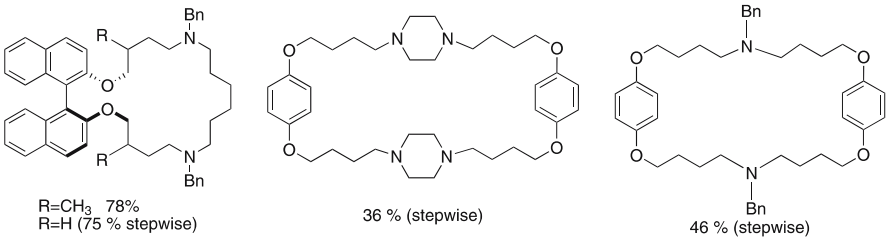
Olefin	Amine	Product	Yield
			85%
			72%
			79%
			49%

Macrocycles can be synthesized conveniently using rhodium-catalyzed hydroaminomethylation of α,ω-diolefins in the presence of primary amines or secondary α,ω-diamines [60–63]. In comparison to common strategies this methodology is a very efficient synthetic route to substituted macrocyclic polyamines with high variability. 12- to 36-membered macrocycles can be obtained from (hetero)diallylic systems in up to 78% yield. In addition, such macrocyclic systems can be debenzylated and the resulting macrocyclic diamines undergo a second ring-closing bis(hydroamino-methylation) to give cryptand systems (Scheme 15) [60, 61].

More recently macrocycles with rigid and flexible aromatic and chiral binaphthyl systems with interesting fluorescence properties have been synthesized via hydroaminomethylation (Scheme 16) [62, 63].



Scheme 15 Hydroaminomethylation in the synthesis of macrocyclic cryptands

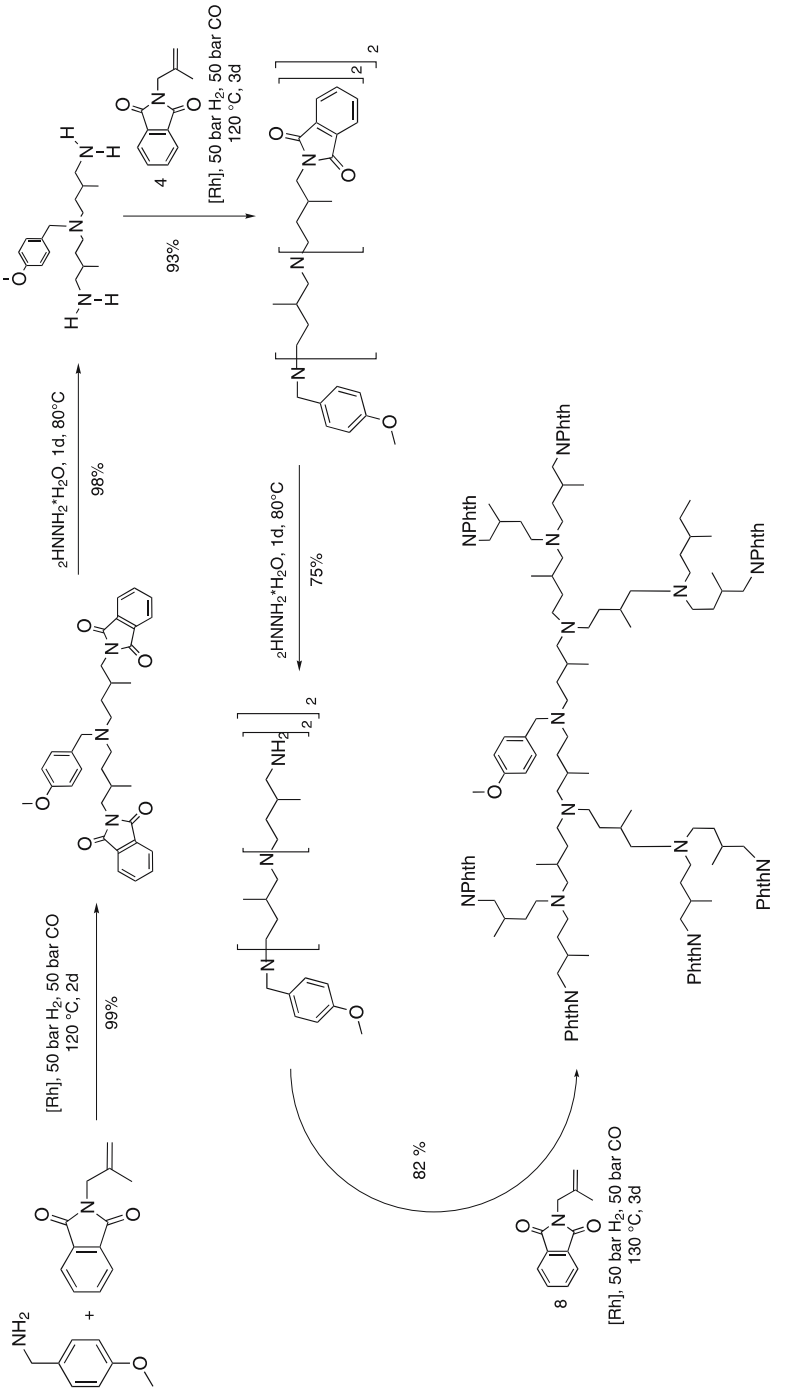


Scheme 16 Hydroaminomethylation in the synthesis of macrocycles

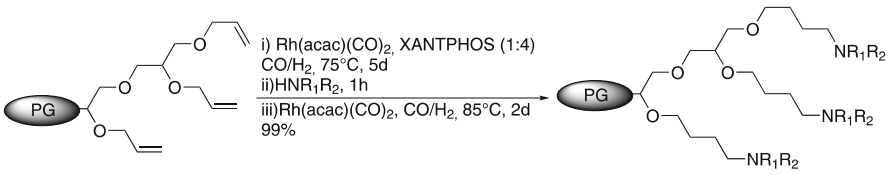
Hydroaminomethylation is also be used for the construction of dendrimers [64]. Here divergent and convergent strategies with wide variabilities can be used. A selected example is shown in Scheme 17.

Sequential hydroformylation/reductive amination of dendritic perallylated polyglycerols with various amines in a one-pot procedure to give dendritic polyamines in high yields (73–99%). Furthermore, the use of protected amines provides reactive core-shell-type architectures after deprotection. These soluble but membrane filterable multifunctional dendritic polyamines are of high interest as reagents in synthesis or as supports in homogeneous catalysis as well as nonviral vectors for DNA-transfection (Scheme 18) [65].

General Procedure for the Stepwise Hydroformylation/Reductive Amination on Allylated Hyperbranched Polyglycerols (PG). Synthesis of Hydroaminomethylated Hyperbranched PG-dendrimers. PG-Allyl, $Rh(acac)(CO)_2$ and XANTPHOS were dissolved in dry toluene and placed in an autoclave. The autoclave was pressurized with CO/H_2 (1 : 1, 30 bar), heated at 70 °C for 5 d. After cooling, the amine was added to the crude PG-aldehyde (1H NMR was used to confirm full conversion) and stirred for 1–2 h. After stirring, $Rh(acac)(CO)_2$ was added and the autoclave was pressurized with CO/H_2 (1 : 6, 70 bar) and heated at 85 °C for 2–5 days. After cooling, the solvent was removed in vacuo and the crude mixture was purified by dialysis (benzoylated cellulose tubing) to give the re-



Scheme 17 Hydroaminomethylation in the synthesis of dendrimers



Scheme 18 Amination of allylated hyperbranched polyglycerols via hydroaminomethylation

spective dendritic polyamine. Dialysis performed in 2-L beaker charged with $CHCl_3$ and stored over 24 h, and after this time solvent was exchanged.

In a similar manner, polymers with unsaturated chains or side chains can be converted to polyamines [66–69]. Conjugated diolefins usually undergo hydroformylation with low selectivities [70]. Mostly hydrogenation of at least one double bond occurs and mixtures of various saturated and unsaturated amines and diamines are obtained [71]. Similar to alkenes also alkynes may serve as unsaturated compounds in hydroaminomethylation reaction sequences. Although synthetically attractive, only a few investigations towards hydroformylation and hydroaminomethylation of alkynes in the presence of *N*-nucleophiles are known. Usually a preferred transformation to furanonic derivatives is observed under hydroformylation conditions [27].

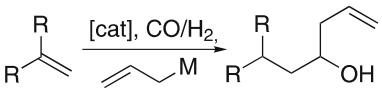
3
Additional *C,C*-Bond Formation of Aldehydes Obtained via Hydroformylation

Among all tandem hydroformylation sequences the ones involving additional *C,C*-bond formations are the most synthetically valuable tandem hydroformylation sequences. These *C,C*-bonds can be formed by adding nucleophiles, which attack the carbonyl carbon, or by adding electrophiles, which attack the α-position. Furthermore, tandem reactions in which the aldehyde or an aldehyde derivative is involved in sigmatropic rearrangement are described.

3.1
Using Carbonyl Reactivity

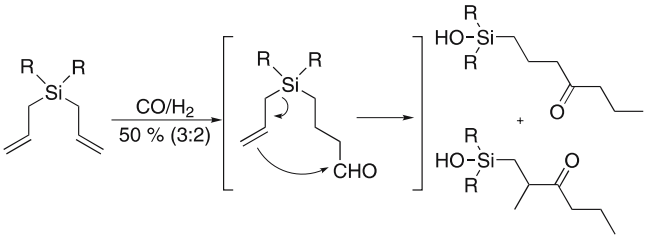
3.1.1
Hydroformylation/Allylation

Allylsilanes and allylboranes are allyl anion equivalents, which are stable enough to be included in subsequent allylation reactions of aldehydes under



Scheme 19 Basic principle for the hydroformylation/allylation

hydroformylation conditions (Scheme 19). The aldehyde obtained from a hydroformylation of bisallylsilanes for example undergoes intramolecular Sakurai reaction to an intermediate homoallylic alcohol. Double bond migration to an enol results in the final ketone product (Scheme 20) [72] (Bärfacker L, Eilbracht P, personal communication).

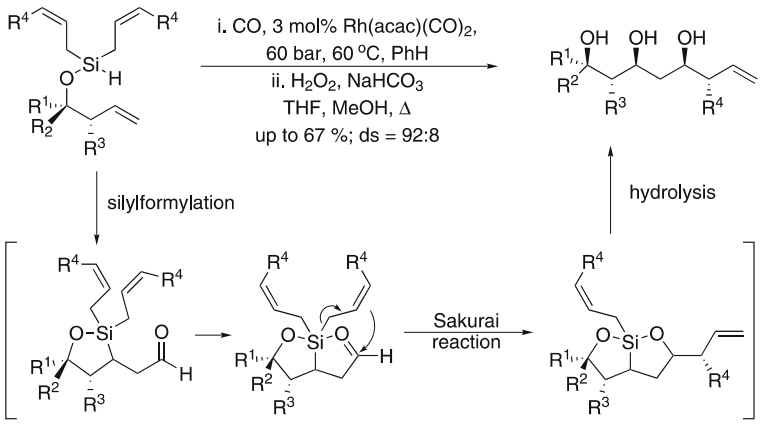


Scheme 20 Hydroformylation/intramolecular Sakurai reaction

In this context, the silylformylation is an interesting alternative to the hydroformylation. Here, hydrogen is replaced with silanes, allowing the formation of an additional carbon-silicon bond and a control of stoichiometry. Silylformylation of a homoallylic bisallylic siloxane gives for example a β-silyl-aldehyde, which undergoes intramolecular Sakurai reaction. The sequence stops at this stage since no further formylation of olefin moieties is possible, due to a lack hydrogen equivalent. Instead, subsequent oxidative work-up and hydrolysis gives valuable polyol fragments for polyketide/macrolide synthesis (Scheme 21) [73, 74].

This tandem intramolecular silylformylation/Sakurai reaction has successfully been applied in a formal total synthesis of mycoticin A [75]. The scope and utility of these reactions was expanded to (*Z*)- and (*E*)-crotyl groups leading to the stereospecific incorporation of both *anti* and *syn* propionate units into the growing polyol chain (Scheme 21) [76].

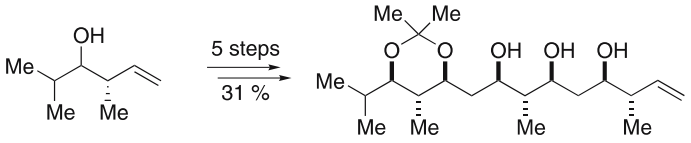
General Procedure for the Silylformaltion/Sakurai Allylation. Synthesis of Polyol Fragments for Polyketide and Macrolide Synthesis. In a magnetically stirred stainless-steel Parr bomb the substrate (1 eq) is dissolved in benzene. The solution is cooled to – 78 °C until frozen. $Rh(acac)(CO)_2$ (3 mol %) is then added and the Parr bomb is assembled and pressurized with CO (60 bar) and vented. This purge is repeated twice and the Parr bomb is pressurized with CO (60 bar) at – 78 °C. The apparatus is then immersed in an oil bath and heated at 60 °C for 22–24 h. After cooling to 0 °C, the bomb is vented. The solution



Scheme 21 Synthesis of polyol fragments via silylformylation/Sakurai reaction

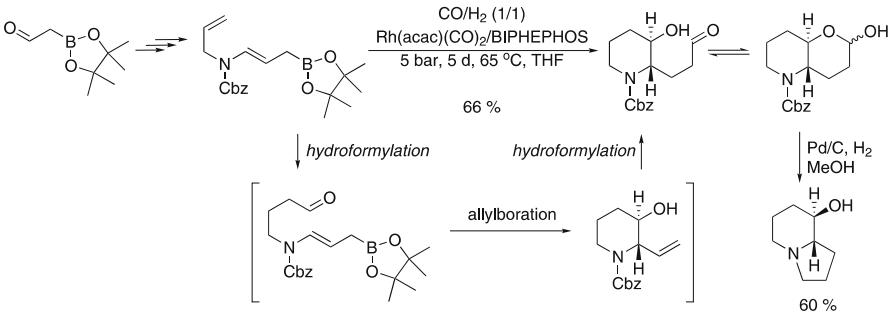
is concentrated and the residue is used without further purification in the Tamao oxidation reaction. The product from the silylformylation/allylation is dissolved in THF/MeOH (1 : 1). To this solution is added $NaHCO_3$ (1.5 eq), followed by H_2O_2 (30 wt % in H_2O, 15 eq). The flask is then fitted with a reflux condenser and the solution is heated for reflux for 30–60 min. The solution is cooled to room temperature and NaS_2O_3 (solution in H_2O) is added. The biphasic solution is filtered through a cotton plug in a separatory funnel and extracted with EtOAc five times. The combined organic layers are dried over $MgSO_4$, filtered, and concentrated. The residue is purified by flash chromatography (silica, EtOAc/hexane).

The power of this methodology is demonstrated with the synthesis of polyketide-like structures by repetitive application of the same procedure (Scheme 22) [76].



Scheme 22 Application of the silylformylation/Sakurai reaction in the synthesis of polyketides

In a similar fashion, allylboronates can be used as allylation reagents under hydroformylation conditions. Thus condensed 1,5-oxazadecalin systems are achieved via tandem hydroformylation/allylboration/hydroformylation sequences starting from an *N*-allyl-γ-amidoallylboronate (Scheme 23) [77, 78]. The aldehyde obtained from a regioselective hydroformylation undergoes diastereoselective intramolecular allylboration to give an intermediate allylic alcohol derivative. The reaction does not stop at this stage, since this

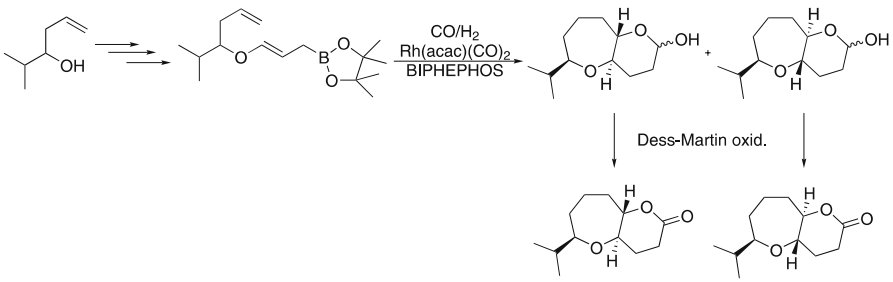


Scheme 23 Hydroformylation/allylboration in the synthesis of hydroindolizines

alkene moiety undergoes a second *n*-selective hydroformylation to give an equilibrium mixture of lactols and an open-chain δ-hydroxy aldehyde. Reductive removal of the Cbz group allows the formation of indolizidine in a further domino-type process consisting of deprotection and reductive amination.

General Procedure for the Hydroformylation/Allylboration/Hydroformylation. Synthesis of γ-hydroxy Aldehydes. BIPHEPHOS (2 mol %) was added to a solution of $Rh(acac)(CO)_2$ (1 mol %) in THF. After stirring for 10 min, a solution of the substrate (1 eq) in THF was added. This mixture was transferred to an autoclave, adding THF in the transfer. The autoclave was heated to 60 °C for 4 days under CO/H_2 (1 : 1, 5 bar). The contents were diluted with MTBE and the mixture was extracted with $NaHCO_3$ (saturated in H_2O). The aqueous phase was extracted with MTBE three times. The combined organic phases were dried over Na_2SO_4 and concentrated. Flash chromatography (silica, cyclohexane/MTBE 3 : 1) furnished a 1 : 1 anomeric mixture of open chain γ-hydroxy aldehyde and the corresponding lactols as a colorless oil.

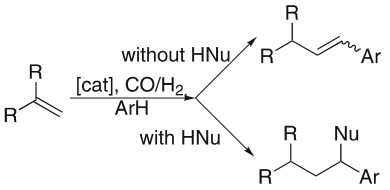
In almost the same manner *trans*-disubstituted hydrooxepans can be obtained from a tandem hydroformylation/allyl boration of (*E*)-alkoxyallylboronates as a mixture of anomers (Scheme 24) [79].



Scheme 24 Hydroformylation/allylboration in the synthesis of oxepans

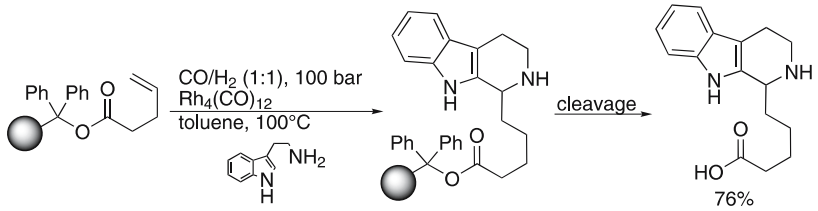
3.1.2 Hydroformylation/Aromatic Substitution

Aldehydes and imines derived from them can undergo electrophilic attack of activated aromatic systems under harsh hydroformylation conditions (Scheme 25).



Scheme 25 Basic principle of the hydroformylation/aromatic substitution

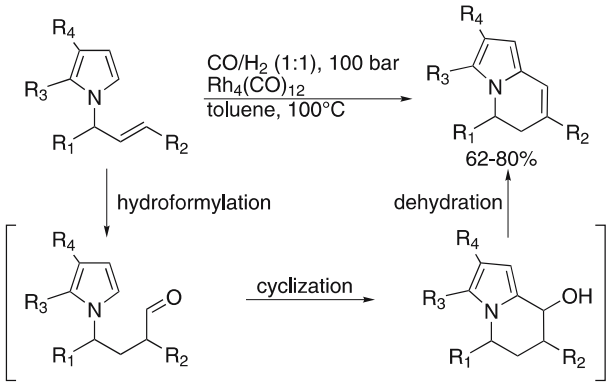
Thus β-carbolines can be obtained in a tandem hydroformylation/Pictet–Spengler-type intramolecular electrophilic aromatic substitution of polymer bound olefins (Scheme 26) [80].



Scheme 26 Hydroformylation/Pictet–Spengler reaction on solid phase – Access to β-carbolins

In a similar fashion, hydroformylation of *N*-allyl-pyrrols leads to 5,6-dihydroindolizines via a one-pot hydroformylation/cyclization/dehydration process (Scheme 27) [81, 82]. The cyclization step represents an intramolecular electrophilic aromatic substitution in α-position of the pyrrole ring. This procedure was expanded to various substrates bearing substituents in the allyl and in the pyrrole unit.

General Procedure for the Hydroformylation/Electrophilic Substitution. Synthesis of 5,6-dihydroindolizines. A solution of 1-allylpyrroles (1 eq) and $Rh_4(CO)_{12}$ (1 mol %) in toluene was introduced by suction into an evacuated stainless-steel reaction vessel. CO (60 bar) was introduced, the autoclave was then rocked, heated to the desired temperature and H_2 (60 bar) was introduced rapidly. When the gas absorption reached the value corresponding to the fixed conversion, the reaction mixture was siphoned out. The degree of conversion and the product distributions were determined by GC and GC-MS, by using acetophenone as an internal standard.

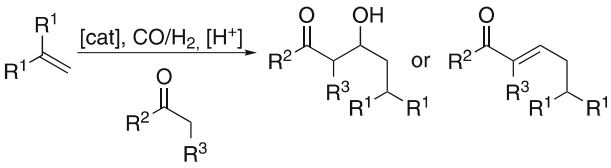


Scheme 27 Synthesis of dihydroindolizines via hydroformylation/aromatic substitution

3.2
Using α-CH-Acidity

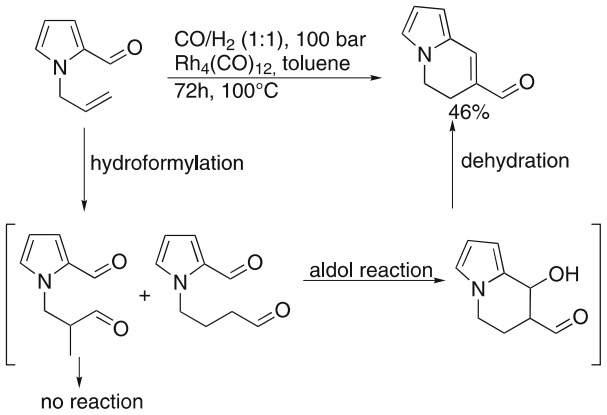
3.2.1
Hydroformylation/Aldol Reaction

The aldol reaction is probably one of the most important reactions in organic synthesis. In many industrially important hydroformylation processes self-condensation of aldehydes is observed. Sometimes this consecutive reaction is favored as in the production of 2-ethyl hexanol. But synthetic applications of tandem hydroformylation/aldol reactions seem to be limited due regioselectivity problems of a mixed aldol reaction (Scheme 28). However, various tandem hydroformylation/intramolecular mixed aldol reactions have been described.



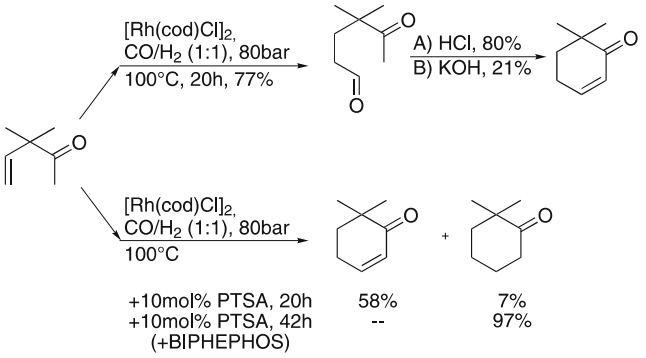
Scheme 28 Basic principle of the hydroformylation/aldol reaction

For example, rhodium catalyzed hydroformylation of 2-formyl-*N*-allyl-pyrrol gives an approx. 1 : 1 mixture of *iso*- and *n*-aldehydes. The latter cyclizes immediately in an aldol reaction followed by dehydration giving 7-formyl-5,6-indolizine in up to 46% (Scheme 29) [83]. Since here only one of the aldehyde groups can act as the enolate nucleophile this cyclization proceed with high regioselectivity (Scheme 29).



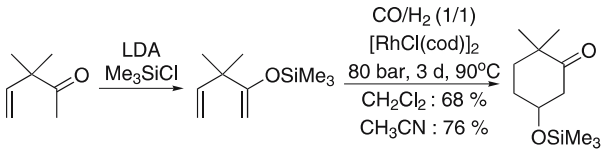
Scheme 29 Synthesis of dihydroindolizines via hydroformylation/aldol reaction

In almost the same manner, tandem hydroformylation/aldol condensation aldol condensation of ketoolefins, such as β,γ-unsaturated ketones, gives a single cyclization product under acid catalysis. Similar to the stepwise reaction, the in situ generated aldehyde preferentially acts as the electrophilic carbonyl component, while the ketone acts as the nucleophilic enol to form the five-membered ring product. Subsequent dehydration and hydrogenation of the resulting enone readily occurs under the reductive reaction conditions used (Scheme 30) [84].



Scheme 30 Hydroformylation/aldol reaction

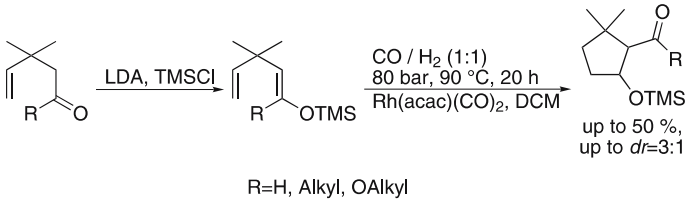
Although the saturated ketone can be obtained in nearly quantitative yields, the loss of synthetically valuable functionality is unfavorable and can be overcome by a modification of the tandem sequence. The use of the corresponding unsaturated silyl enol ethers in a tandem hydroformylation/Mukaiyama aldol reaction gives the desired aldol adduct with complete



Scheme 31 Hydroformylation/Mukaiyama aldol reaction

transfer of the silyl group to aldol hydroxyl group (Scheme 31) [84, 85]. Obviously the less substituted double bond is hydroformylated selectively resulting in a regioselective tandem reaction.

This method can also be applied to silyl enol ethers of homologous unsaturated ketones as well as of unsaturated aldehydes or esters [85–87]. While unmodified unsaturated esters give only the corresponding aldehydes without cyclization under tandem hydroformylation/aldol reaction conditions, the corresponding silylated ester enolates smoothly cyclize in a tandem hydroformylation/ Mukaiyama aldol reaction (Scheme 32) [85–87].

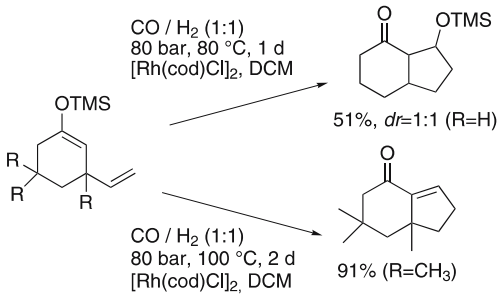


Scheme 32 Unsaturated aldehydes, ketones and esters in the hydroformylation/Mukayama aldol reaction

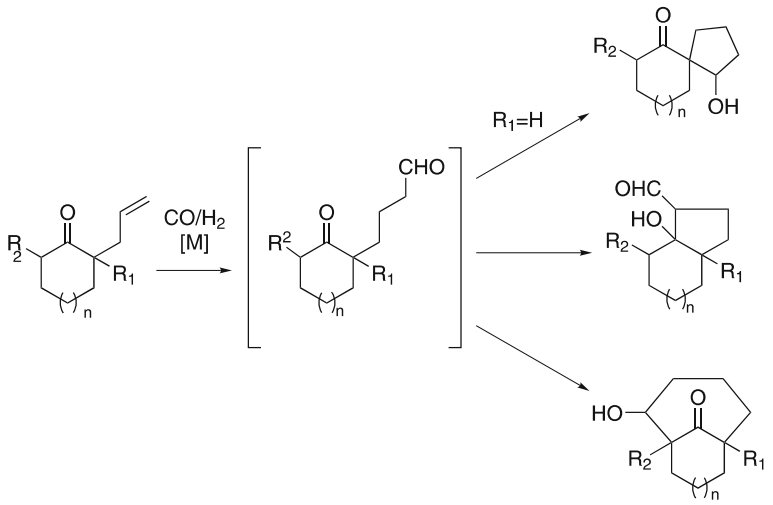
These examples clearly demonstrate that unsaturated carbonyl compounds can act as precursors for dicarbonyl systems. While the preexisting and less reactive carbonyl or carboxyl unit can conveniently be activated to serve as the enolate unit in aldol reactions the following hydroformylation step generates a second more reactive (aldehyde) carbonyl group in situ. Thus incorporation of the hydroformylation in the aldol reaction can be used to differentiate between carbonyl groups of different reactivity and to activate selectively the less reactive one as enolate allowing to perform an effective chemo-, regio-, and stereocontrol of the aldol cyclization immediately following the hydroformylation step [86, 87].

Similarly, tandem hydroformylation/aldol sequences can be applied to the formation of bicyclic and spirocyclic compounds. Thus silyl enol ethers of 3-vinyl and 3-allyl cycloalkanones give ring anellated products (Scheme 33) [86, 87].

Applying the same methods to 2-allylcycloalkanones can in principle lead to three different aldol products (Scheme 34). While the spiro compound is



Scheme 33 Bicyclic aldols and enones via hydroformylation/aldol reaction

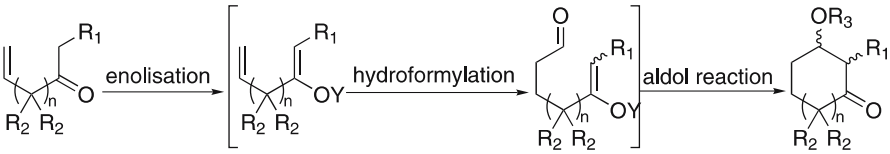


Scheme 34 Hydroformylation/aldol reaction

usually preferred, as already demonstrated [85], the use of various methods, such as regiodirecting and/or reversibly blocking ester groups or the above-described use of enolate equivalents are available to achieve high regioselectivity [86, 87].

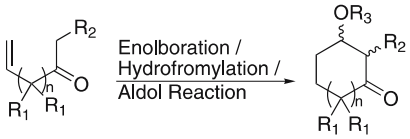
Very recently, a tandem sequence consisting of enolboration/hydroformylation/aldol reaction has been described [88]. Here configuration of the enol boronate is transferred to the aldol product, allowing good to excellent diastereoselectivities in the hydroformylation/aldol reaction. With this method, 5–7-membered rings are obtained in excellent yields (Scheme 35).

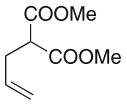
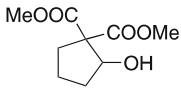
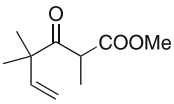
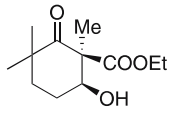
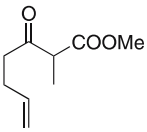
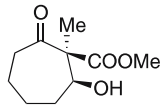
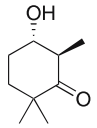
General Procedure for Sequential Enolboration/Hydroformylation/Aldoladdition. Synthesis of Cyclic Aldol Products. NEt_3 (1.05 eq to carbonyl compound) was precomplexed under an argon atmosphere with $(cy\text{-hex})_2BCl$ (1.05 eq) in dry CH_2Cl_2 at 0 °C for 15 min. The unsaturated carbonyl compound was then added slowly via syringe and the enolbo-



Scheme 35 Enolboration/hydroformylation/aldol reaction – Diastereoselective access to cyclic aldols

Table 3



Olefin	Product	Yield	*dr*
		51%	—
		51%	2.5 : 1
		51%	6 : 1
		51%	20 : 1

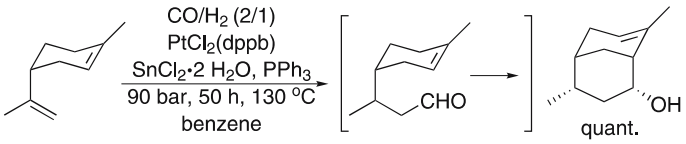
ration was allowed to stir for an additional 30 min. The mixture was simply transferred into the autoclave containing $Rh(acac)(CO)_2$ (0.9 mol %) and solvent. The autoclave was then pressurized with CO/H_2 (1 : 1, 60 bar) and heated overnight to 80 °C. Upon cooling the autoclave to rt, the reaction mixture was removed and concentrated under reduced pressure. Enough MeOH was added to dissolve the solid residue along with a small amount of conc. pH 7 phosphate buffer and H_2O_2 (30 wt % in H_2O), and the reaction was allowed to stir overnight before being extracted with Et_2O, washed with $NaHCO_3$ (saturated in H_2O), dried and concentrated prior to further purification when necessary via flash chromatography or Kugelrohr distillation.

3.3
Involving Sigmatropic Rearrangements

Hydroformylations can also be combined with sigmatropic rearrangements. Here the carbonyls or derivatives derived from them are incorporated in a pseudo aromatic cyclic transition state.

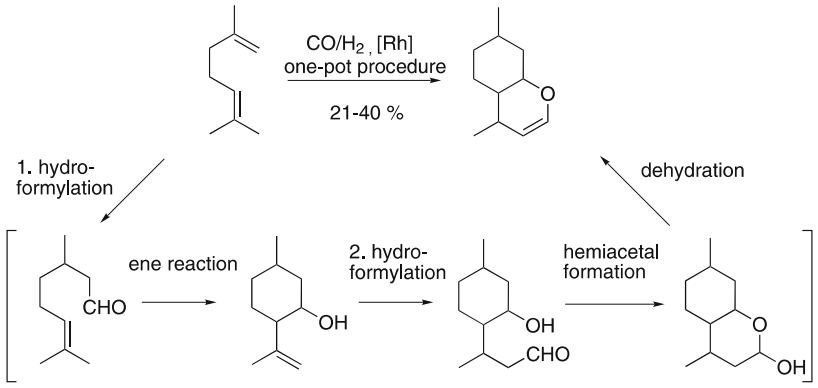
3.3.1
Hydroformylation/Carbonyl Ene Reaction

A tandem hydroformylation/carbonyl ene reaction can be observed in cases, in which substrates with at least two isolated olefinic bonds are hydroformylated at only one double bond selectively. Thus hydroformylation of limonene with $PtCl_2(PPh_3)_2/SnCl_2/PPh_3$ or $PtCl_2$(diphosphine)$/SnCl_2/PPh_3$ gives a mixture of two diastereomeric alcohols upon carbonyl ene reaction of the intermediate aldehyde, (Scheme 36). Best results are achieved with a $PtCl_2$(dppb) complex. The mechanism of the final intramolecular cyclization step resembles an acid catalyzed carbonyl ene reaction [89].



Scheme 36 Hydroformylation/carbonyl ene reaction

In some cases, the resulting olefin is not inert and undergoes consecutive hydroformylation. If aliphatic 1,5-dienes are subjected to a hydro-



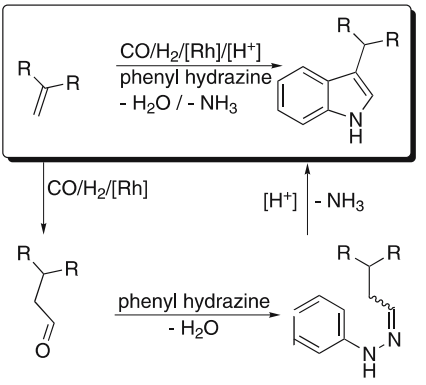
Scheme 37 Synthesis of chromanes via hydroformylation/carbonyl ene reaction

formylation the less substituted double bond is hydroformylated preferably. Subsequent carbonyl ene reaction gives an homoallylic alcohol which is further hydroformylated. Acetalization and dehydration gives the chromane derivative in an overall tandem hydroformylation/carbonyl ene reaction/hydroformylation/acetalization/dehydration, (Scheme 37) [90].

General Procedure for the Hydroformylation/Carbonyl ene Reaction/*O,O*-acetal Formation/Dehydration. Synthesis of Chromane Derivatives. A solution of the substrate (1 eq) $RhCl(PPh_3)_3$ (1 mol %) and PPh_3 (3 mol %) in dry dioxane was heated for 70 h to 120 °C und an atmosphere of CO/H_2 (1 : 1, 100 bar). The crude product was filtered through basic alumina (eluated with MTBE). After evaporation of the solvent further purification by column chromatography (silica, PE/MTBE) furnished the title compounds.

3.3.2 Hydroformylation/Fischer Indole Synthesis

If the hydroformylation of olefins is conducted in the presence of aromatic hydrazines and Brønsted or Lewis acids indoles can be obtained directly in one pot [91–93, 95]. Hydroformylation of the olefin gives an intermediate aldehyde, which is trapped immediately by the present aromatic hydrazine as an aromatic hydrazones similar to the formation of imines under hydroformylation conditions. Under acid mediation these aromatic hydrazones undergo a Fischer indolization, consisting of a [3,3]-sigmatropic rearrangement followed by a cyclization and elimination of ammonia (Scheme 38).



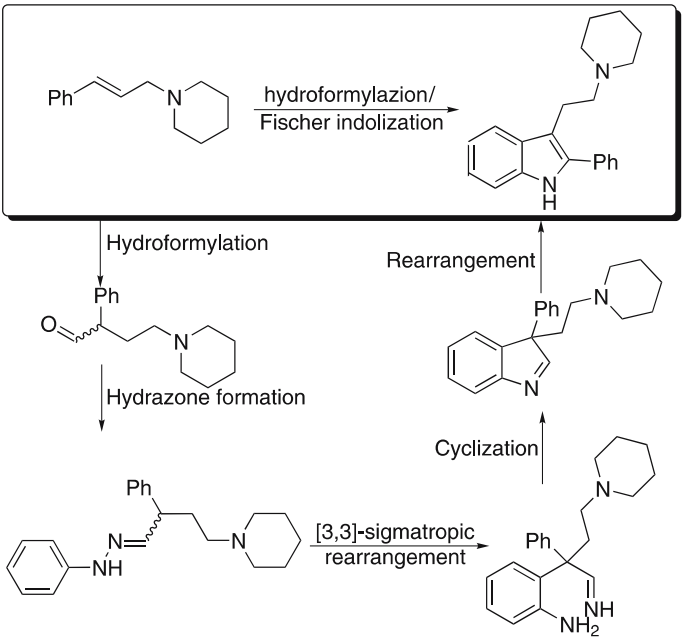
Scheme 38 Hydroformylation/Fischer indole synthesis

With this tandem hydroformylation/hydrazone formation/Fischer indolization 3-substituted indoles such as valuable intermediates for the synthesis of pharmaceuticals as well as pharmaceuticals can be obtained in a very

convenient fashion [94]. In many cases this tandem reaction can be conducted in aqueous sulfuric acid be using water soluble hydroformylation catalysts such as rhodium/TPPTS or rhodium/SulfoXANTPHOS [95]. Chiral information within the starting olefin is conserved and the relative configuration of newly formed stereocenters can be controlled by the use of a catalyst directing auxiliary as Breit has used for diastereoselective tandem hydroformylation [96] (Schmidt AM, Eilbracht P (2005) personal communication).

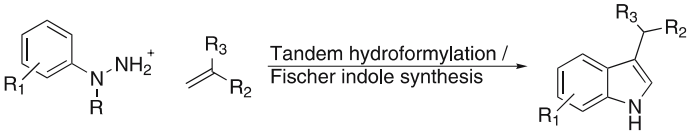
General Procedure for the Hydroformylation/Fischer Indole Synthesis. Synthesis of Tryptamine Derivatives in Water. Aminoolefin (1 eq), aromatic hydrazine (1 eq), $Rh(acac)(CO)_2$ (0.3 mol %) and TPPTS (1.5 mol %) are dissolved in H_2SO_4 (4 wt % in H_2O, 2.5 wt % olefin), filled in an autoclave and pressurized with 10 bar H_2 and 50 bar CO. After stirring for 3 days at 100 °C ammonia (30 wt % in water) is added and the mixture is extracted with EtOAc. The solvent is evaporated to give the product which purified by column chromatography (silica, CH_2Cl_2, ^iPrOH, NEt_3) if necessary.

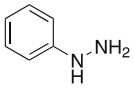
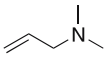
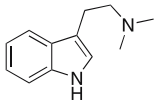
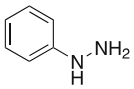
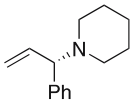
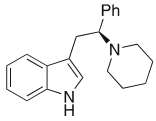
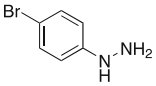
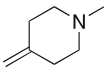
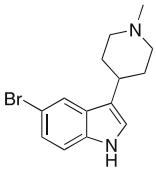
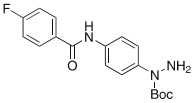
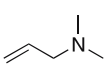
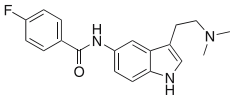
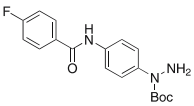
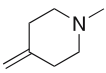
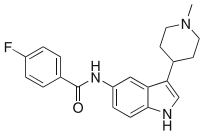
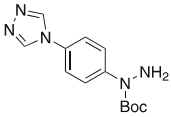
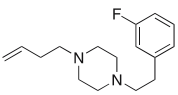
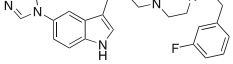
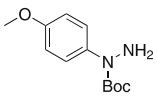
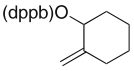
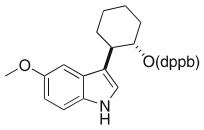
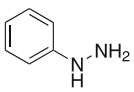
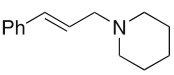
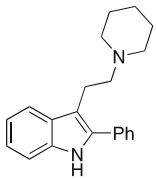
Even 2,3-disubstituted indoles can be achieved if internal olefins are used. Regioselective hydroformylation of a styrene-type olefin and subsequent hydrazone formation and Fischer indolization gives an intermediate indole with a quaternary center in 3-position. The regained aromaticity is the driving force for the rearrangement of one substituent into the 2-position of the indole core (Scheme 39).



Scheme 39 Rearrangement involved in hydroformylation/Fischer indole synthesis – Access to 2-aryl tryptamines.

Table 4 Pharmacologically relevant indole derivatives via hydroformylation/Fischer indole synthesis



Hydrazine	Olefin	Product	Yield
			quant.
			54%, 95% ee
			quant.
			44%
			95%
			51%
			44%, *dr* > 95 : 5
			60%

4 Conclusions

In conclusion, the applicability of the transition metal catalyzed hydroformylation of easily accessible functionalized or non-functionalized unsaturated compounds is expanded by its implementation in reaction sequences, tandem reactions or domino reactions. The hydroformylation can be combined with simple functional group transformations, such as reduction or isomerization, or with *C*,*O*-, *C*,*N*- and, most importantly, *C*,*C*-bond forming reactions. It can be expected that more interesting examples and applications will be presented in the future.

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