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Rh Catalyzed Multicomponent Tandem and one-pot Reactions under Hydroformylation Conditions

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Hydroformylation
Rhodium catalysis
Multicomponent reactions
Homogeneous catalysis

Abstract

The hydroformylation reaction represents one of the most important metal catalyzed bulk chemical manufacturing processes today. However, tremendous progress towards more complex molecules using tandem hydroformylation has been achieved during the past decade. Different approaches towards indoles and other nitrogen containing heterocycles, alkaloids, and other biologically active compounds are steadily turning hydroformylation into one of the methods to be considered even in the complex syntheses of natural products and other fine chemicals. The application of organocatalyzed processes coupled with formation of aldehydes through hydroformylation reaction in the synthesis of enantioenriched fine chemicals is another turning point in the application of this reaction. Vast number of other new reaction sequences under hydroformylation conditions have been developed turning tandem and one pot sequences under hydroformylation conditions into a method of choice for organic chemistry and catalysis practitioners.

Contents

1. Introduction

The hydroformylation reaction is defined as the reaction of an olefin with carbon monoxide and hydrogen, affected by a late transition metal catalyst to give a homologous aldehyde. Since its discovery by O. Roelen in 1938, [1-3] the hydroformylation reaction has become a useful tool for the synthesis of aldehydes, representing one of the most important chemical manufacturing processes today with capacity amounting to more than 9 million tons of hydroformylated products worldwide per year [4, 5].

In addition to industrial aspect, the hydroformylation of olefins is an attractive synthetic transformation; the reaction introduces the synthetically useful aldehyde function, which prepares the product for additional carbon skeleton expanding operations. The reaction requires only catalytic amounts of a late transition metal catalyst, with rhodium(I)complexes being the most active and selective catalysts for this reaction.

From the synthetic point of view aldehydes obtained from olefins under hydroformylation conditions are usually converted to more complex reaction products in a tandem or domino fashion involving hetero functionalization of aldehydes to form acetals, aminals, imines and enamines, and further reactions stemming from those intermediates. 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 arom. substitutions, including Fischer indole syntheses.

Coupled catalytic processes (tandem, domino, one-pot) are of great interest in this area of catalysis due to several reasons:

1) Inertness of olefinic group which can be carried through multiple steps under various reaction conditions.

2) Compatibility of hydroformylation conditions with many other functional groups or reagents present at the outset of the reaction.

3) Versatile chemistry of the aldehyde group, which can be further converted via reduction, oxidation, or other reactions to give alcohols, amines, carboxylic acid derivatives, aldol condensation products, and many others.

4) Tunability and versatility of Rh catalysts and ligands used in multistep sequences.

Numerous reviews on synthetical and industrial use [6-12], mechanistic aspects [14, 15], and asymmetric/enantioselective versions [16-21] of hydroformylation are available. A review by Eilbracht et al. (highly comprehensive to the end of 1998) described domino or tandem reactions in which all steps are carried out under hydroformylation conditions [23]. Several dozen examples of tandem catalysis are included. Given this coverage, and more recent examples appearing in 2003 [24] by Breit and more recently in 2004 [25, 26] and 2006 [27] by Eilbracht which only covered few examples of domino processes under hydroformylation conditions, this review shall comprehensively focus on examples emerging in the past decade (2005-2015). Review comparing conventional and tandem processes under hydroformylation

conditions appeared in 2010 [28] in the same time as the review on microwave-assisted domino hydroformylation/cyclization reactions [29].
In present review comprehensive overview of all new reaction types and progress in the field with emphasis on useful synthetic targets and novel mechanistic approaches will be discussed. Examples of two or more step conversions of unsaturated compounds under Rh catalyzed hydroformylation conditions involving initial hydrocarbonylation and additional conversions of intermediates are presented.

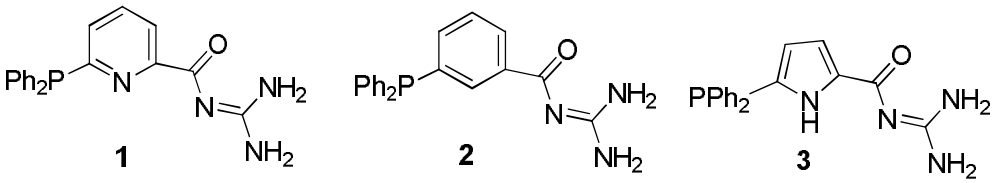
2. Tandem Hydroformylation–Hydrogenation (C-H bond formation)

Linear 1-alkanols (n-alcohols) are widely used in industry as solvents and precursors of detergents and plasticizers. Direct and selective conversion of terminal alkene into n-alcohol by anti- Markovnikov hydration would be an ideal process [30]. However, current industrial production of n-alcohols mostly employs a multiple-step processes consisting of hydroformylation of terminal alkenes, purification of n-aldehydes, and then hydrogenation of n-aldehydes to n-alcohols. One-pot hydroformylation/hydrogenation process would be advantageous because it simplifies the process operation and syngas (a mixture of H_2 and CO) can be directly used for hydrogenation without the need of using pure hydogen gas. The tandem hydroformylation/hydrogenation has been investigated for a long time using Co-, [31, 32] Rh-[33-36], Ru-[37-39], and Pd-[40, 41], based systems. Although these tandem systems gave a mixture of *n*- and *i*-alcohols in good yields (mostly >90%), a significant amount of alkane was often obtained as a byproduct. In addition, another problematic issue is the low normal/iso selectivities (n/i < 10) in the hydroformylation step, causing low *n*-alcohol yields.

2.1 Supramolecular catalyst system

Breit group designed novel supramolecular catalytic system based on Rh metal and bifunctional ligands **1-3** that combined the structural features of phospine ligand (metal binding unit) with an acyl guanidinium functionality for the recognition of carboxylate groups (Scheme 1) [42].
A rhodium catalyst based on this ligands was also successfully applied in the highly regioselective hydroformylation of β,γ-unsaturated carboxylic acids [43], and the decarboxylative hydroformylation of α,β-unsaturated carboxylic acids (see sections 3.6 and 4.1.1) [44].

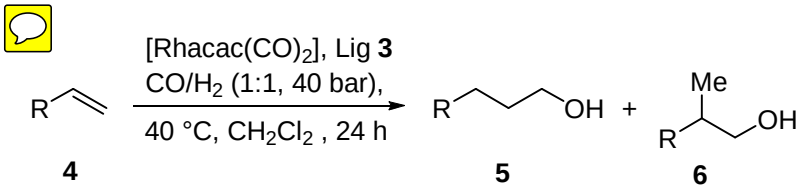
Scheme 1. Bifunctional phosphine-acylguanidinium ligands



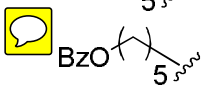
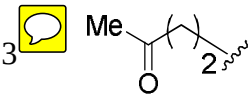
Guanidinium unit operates by hydrogen bonding, hence, decreasing the energy level of the lowest unoccupied molecular orbital (LUMO) of the substrate, and activating the substrate for a transition-metal-catalyzed reaction. Ligand **3** which contains pyrrole NH group as

additional hydrogen bond donor functionality was able to interact stronger with weakly binding neutral host molecules such as aldehydes. Authors were able to convert terminal alkenes **4** (Table 1, entries 1–3) into the corresponding alcohols with good regioselectivities (**5**/**6** up to 92:8) under mild conditions (40 °C, 40 bar CO/H_2). In the case of styrene, the branched alcohol was formed as the major regio isomer (Table 1, Entry 4) which is expected for the styrene case.

Table 1. Tandem Hydroformylation-Hydrogenation

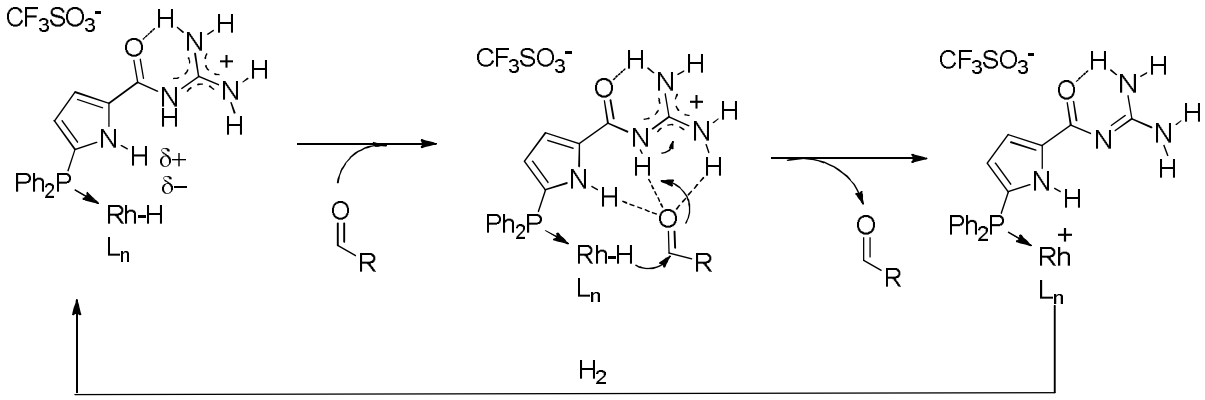


4 **5** **6**

Entry	R	Conversion [%]	Yield [%]	**5**/**6**
1		90	87	92:8
2		95	93	83:17
3		100	98	91:9
4	Ph	95	90	7:93

The key mechanistic step of this transformation involves concerted reduction where the substrate coordinates to the outer sphere of the ligand and not to the metal prior to the addition of dihydrogen. The catalyst provides an acidic (from guanidine) and a hydridic hydrogen atom (at the rhodium center) in a concerted manner. In the next step, the basic guanidine functionality facilitates the heterolytic cleavage of hydrogen and regeneration of the active catalyst (Scheme 2).

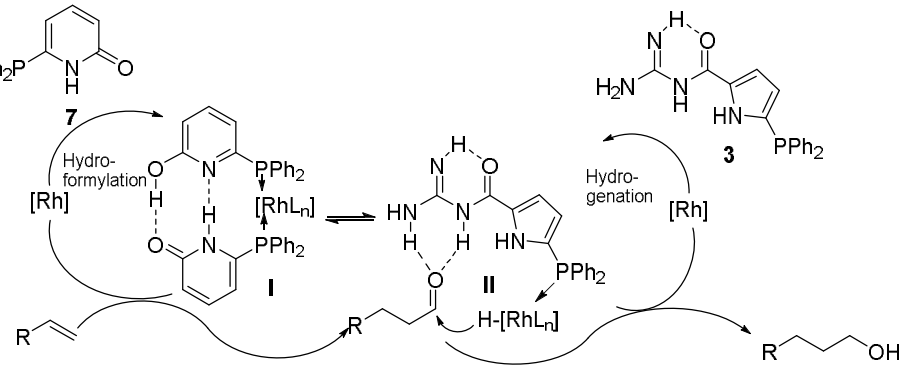
Scheme 2. Proposed hydrogenation mechanism using supramolecular catalyst system



2.2 Cooperative ligand system

While the above system showed high activity, its regioselectivity toward the linear alcohol products was not optimal. To address this issue Breit group introduced multifunctional rhodium catalyst system that enables the simultaneous catalysis of two distinct transformations, controlled by the cooperative action of two different ligands **7** and **3** (Scheme 3) [45]. Ligand **7** (6-DPPon=6- diphenylphosphanylpyridone) has been designed to selfassemble in the presence of a Rh(I) center to form a chelating catalyst system that acts as a highly active and regioselective hydroformylation catalyst [46-51].As already described the acylguanidine ligand **3**, enables highly chemoselective hydrogenation of aldehydes. Simultaneous action of these two catalysts allowed highly selective synthesis of linear alcohols.

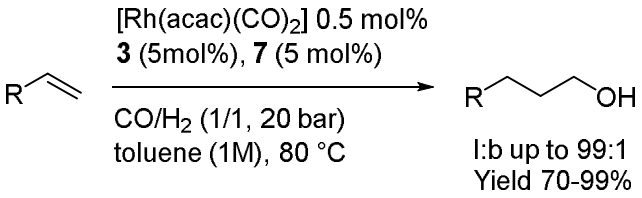
Scheme 3. Cooperative ligand system



Complex **I** catalyzes hydroformylation step exclusively while complex **II** catalyzes hydrogenation step exclusively.

Under optimized conditions up to 99% yield and 99:1 regioselectivity was obtained after 24 hours of reaction Acetals, esters, benzyl and silyl ethers, carbamates, and free hydroxyl groups are well tolerated. Furthermore, 1,2-disubstituted alkenes are completely unreactive under these reaction conditions because of high chemoselectivity for the terminal alkene in the hydroformylation step.

Scheme 4. Cooperative ligand system in the hydroformylation/hydrogenation reaction sequence



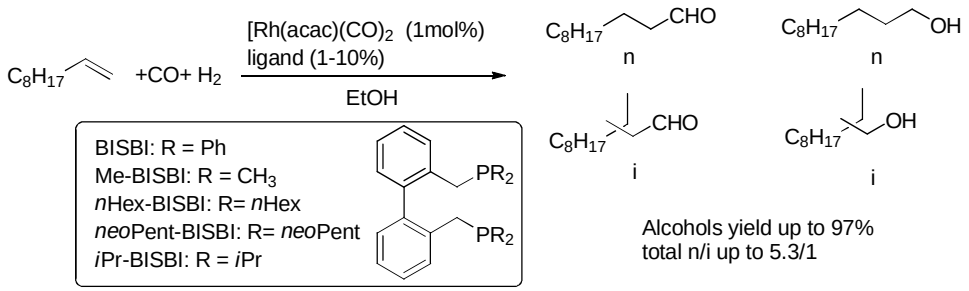
R = Cy, $CH_3(CH_2)_5$, $(CH_2)_4OH$, $(CH_2)_4OTHP$, $(CH_2)_4OBn$, $(CH_2)_4OAc$,$(CH_2)_9OTBS$, $PhNHCO_2(CH_2)_4$

2.3 Bifunctional ligand system

Nozaki and coworkers used a bisphosphine ligand, BISBI, which consists of two diarylmonoalkylphosphine units with the idea to combine the high n/i ratio achieved by

BISBI and high hydrogenation activity of trialkylphosphines for the selective formation of alcohols [52]. Hence, series of alkyl-substituted BISBI analogues were tested in the tandem hydroformylation/hydrogenation reaction (Scheme 5).

Scheme 5. Tandem hydroformylation/hydrogenation with BISBI type ligands

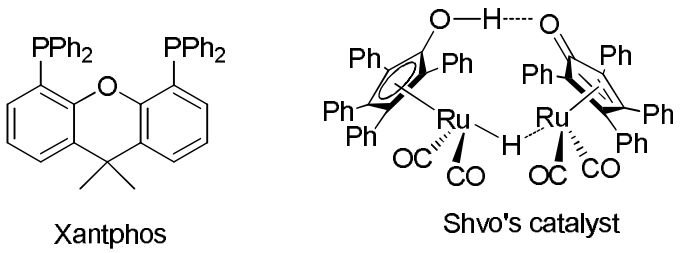


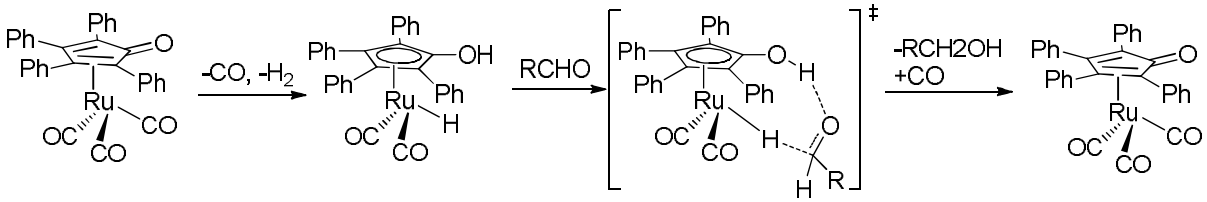
The reaction is a two-step process that consists of hydroformylation of decene and hydrogenation of the resulting aldehyde. The total n/iso values (sum of n-alcohol and n aldehyde/sum of *i*-alcohols and *i*-aldehydes) achieved are in the range of 0.4-5.3) depending on the ligand and reaction conditions, with Me-BISBI being the best performing ligand. The protic solvents turned out to be essential for the reaction as in the aprotic solvents the main product of the reaction is aldehyde with only traces of alcohol obtained.

2.4 Rh/Ru dual catalyst system

While previous approaches relied on the use of a single metal catalyst to perform the two different reactions, here the mixture of two catalysts in one pot was used. Each of these catalyzes one reaction with high efficiency without disturbing the other reaction [53]. Rh/XANTPHOS catalyst was used for the linear-selective hydroformylation step. For aldehyde-selective hydrogenation, a Shvo's catalyst, ruthenium-based ligand–metal bifunctional catalysts were used (Scheme 6).

Scheme 6. Ligands and catalysts used in this study and mechanism of reaction

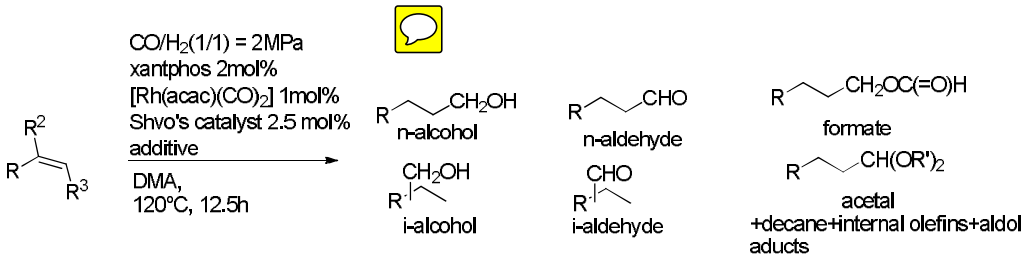




The use of less-polar, aprotic solvents such as toluene and THF resulted in the lower yields of n-alcohol with an increase of dodecyl formate formation. In contrast, a slight improvement in

the yield was achieved in polar aprotic solvents. Reaction temperature was also essential for the product distribution. At 80 °C, both hydroformylation and hydrogenation steps are very slow. At 120 °C and with prolonged reaction time n-alcohol is obtained in 90.1% yield (Table 2).

Table 2. Tandem Hydroformylation/Hydrogenation of decene using Rh/Ru dual catalyst system



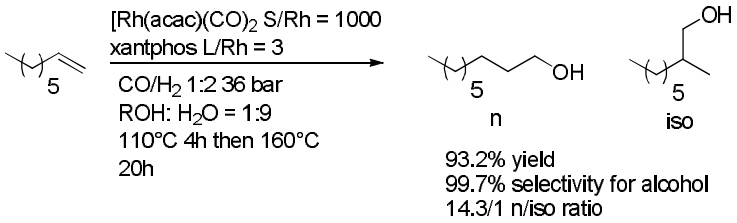
Entry	Substrate (R1, R2, R3)	n-alcohol(%)	n/iso
1	C_8H_{17}, H, H	90	22
2	$HOCH_2$, H, H	31	8.9
3	$AcOCH_2$, H, H	78	>100
4	$HO(CH_2)_2$, H, H	75	32
5	$AcO(CH_2)_2$, H, H	87	16
6	$HO(CH_2)_3$, H, H	95	33
7	$THPO(CH_2)_4$g, H, H	80[f]	16
8	$PhCH2O(CH_2)_4$, H, H	81[f]	20
9	$TBSO(CH_2)_4$h, H, H	80[f]	22
10	(1,3-dioxolan-2-yl)$(CH_2)_8$, H, H	79[f]	19
11	$PhNHCO_2(CH_2)_4$, H, H	75[f]	15
12	cyclohexyl, H, H	87[f]	18
13	C_7H_{15}, CH_3, H,	62[f]	>50
14	C_7H_{15}, H, CH_3	22[i]	0.6
15	Ph, H, H	60	1.5

Kinetic measurements led to the conclusion that the presence of Shvo's catalyst did not affect the rate of hydroformylation by Rh/XANTPHOS but slightly decreased the selectivity [54]. On the other hand, the presence of Rh/XANTPHOS slightly decreases the rate of hydrogenation, but the difference is almost negligible. The reason for this is poisoning of Shvo's catalyst by CO, it was confirmed that Rh/XNTPHOS present in the reaction mixture did not change the rate of hydrogenation by Shvo's catalyst.

2.5 On water reaction with Rh/XANTPHOS catalyst

Vogt et al. reported that Rh/XANTPHOS, which was originally reported as *n*-selective hydroformylation catalyst and does not catalyze hydrogenation, can catalyze this tandem reaction (n alcohol 86%, n/i = 11) in a 1:9 mixture of polar organic solvent and water at high temperatures [55]. Optimized conditions involved use of lower temperature of 110 °C for 4h which beneficially influences the first step of reaction i.e. favors the formation of n product in hydroformylation step, while higher temperature of 160 °C was used subsequently for 20h to promote faster hydrogenation. These reaction conditions could produce an 93.2% yield of 1-nonanol and only octane is formed in traces as a secondary product (Scheme 7).

Scheme 7. Tandem hydroformylation/Hydrogenation of 1-heptene to 1 nonanal

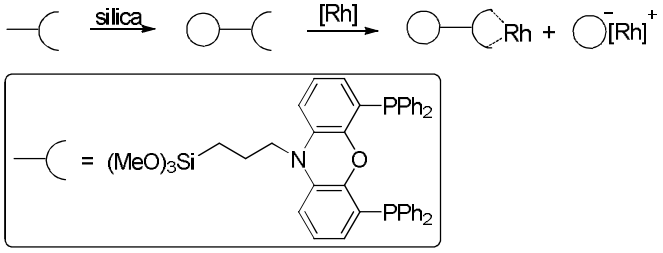


The beneficial effect of water is explained by the fact that this very polar reaction medium pushes the long hydrophobic aliphatic chains together, increasing the local substrate concentration. This was described as ‘‘on water’’ effect by Sharpless et al. in 2005 [56].Also, this very protic and polar medium may favor the formation of cationic rhodium species, known for their good activity in polar multiple bond reductions [57-60].

2.6 Solid support reactions

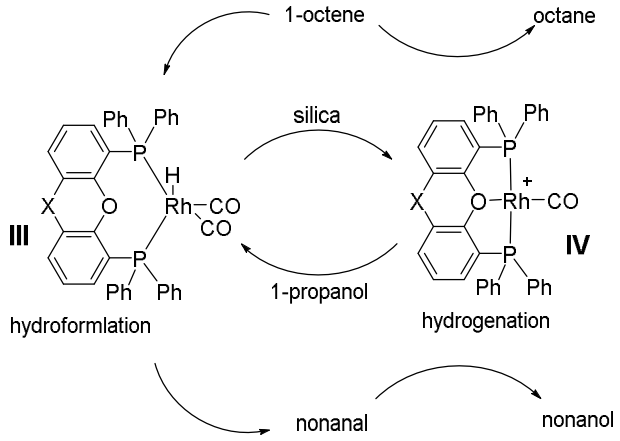
Van Leeuwen et al. covalently tethered homogeneous hydroformylation catalyst designed to produce selectively linear aldehydes, to a polysilicate support using the sol-gel technique and by a direct anchoring to commercially available silica (Scheme 8) [61].

Scheme 8. Anchoring of Rhodium complex to silica support



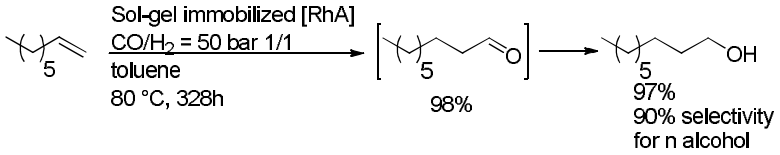
The immobilized transition-metal complex [Rh(**A**)CO]+ , in which **A** is *N*-(3-trimethoxysilane-*n*-propyl)-4,5-bis(diphenylphosphino)phenoxazine, was prepared both via the sol-gel process and by covalent anchoring to silica. Under standard hydroformylation conditions, [Rh(**A**)CO]+ (**III**) and HRh(**A**)$(CO)_2$ (**IV**) coexist on the support (Scheme 9).

Scheme 9. Tandem Hydroformylation/Hydrogynation sequence on Silica support catalyzed by 2 different Rh catalysts present



This dual catalyst system performed as a hydroformylation/hydrogenation sequence catalyst giving selectively 1-nonanol from 1-octene; ultimately, 98% of 1-octene was converted to mainly 1-nonanal and 97% of the nonanal was hydrogenated to 1-nonanol. (Scheme 10)

Scheme 10. Tandem Hydroformylation/Hydrogenation of 1-octene

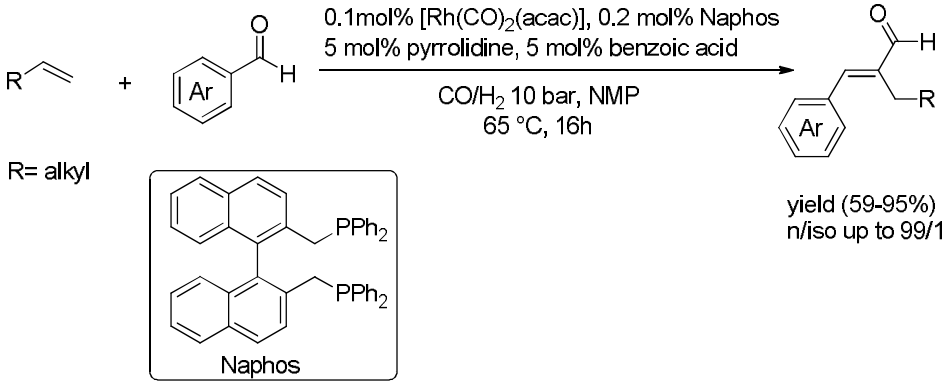


3. Tandem Hydroformylations with Additional C-C Bond Formations

3.1 Tandem hydroformylation/aldol condensation

Aldol reaction is arguably one of the most important C-C bond forming reactions, and while the asymmetric aldol reaction was examined in detail (vide infra) comprehensive contribution on aldol condensation appeared recently. Beller group examined hydroformylation/cross-aldol reaction of olefins with aldehydes which in overall constituted synthesis of α,β-unsaturated aldehydes from olefins [62]. In general, the difficult task in this reaction is to avoid the formation of the homoaldol product, however, judicious selection of solvent (N-methyl-2-pyrrolidone, NMP) led to only traces of homoaldol product and a high yield of the desired crossaldol product was observed. Various olefins and aromatic aldehydes underwent efficient transformation in the presence of a cooperative rhodium/phosphine and organocatalyst system to afford the corresponding α,β-unsaturated aldehydes in good to excellent yields with high E stereoselectivities (Scheme 11).

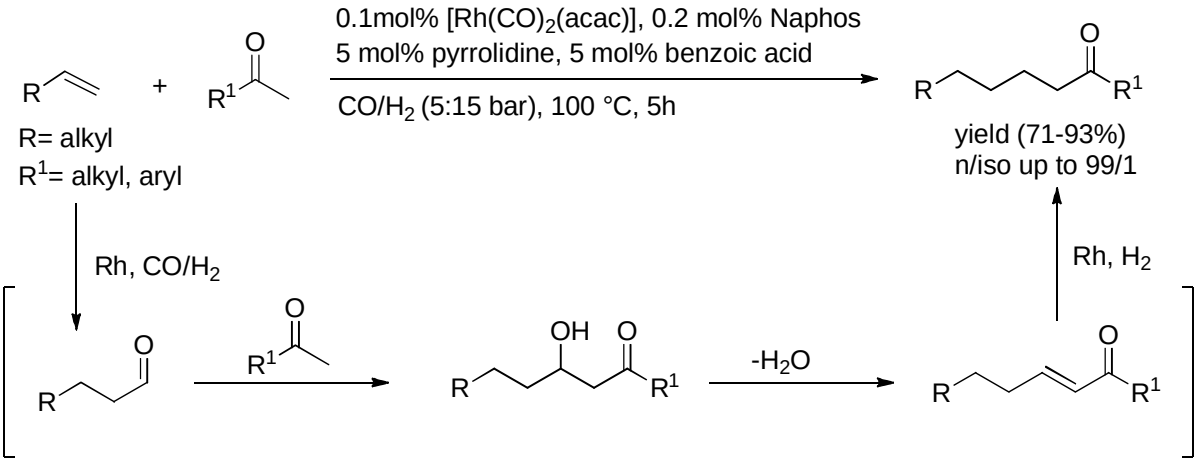
Scheme 11. Domino-Hydroformylation/Aldol Condensation



In order to avoid hydrogenation of obtained products lower temperature of 65 °C was used along with lower partial pressure of H_2 (5 bar, 1/1 ratio to CO)

Beller et al. also developed selective intermolecular domino hydroformylation/aldol condensation/hydrogenation reaction sequence that allowed efficient synthesis of ketones starting from the olefins [63]. Crucial for the success of this sequence is the precise control of both chemo and regioselectivity by the $[Rh(CO)_2(acac)]$/Naphos catalyst. Furthermore, the combination of this catalyst system with an optimal acid–base combination prevented unwanted self-condensation processes. Both short- and long chained terminal aliphatic olefins provided the corresponding saturated ketones in good yields with high regioselectivities (n/iso ratios= >98:2). Acetone as well as other ketones was successfully utilized in these reactions (Scheme 12).

Scheme 12. Domino Hydroformylation/Aldol Condensation/Hydrogenation Catalysis



Here, higher temperature of 100 °C was necessary for the hydrogenation step to take place as well as higher partial pressure of H_2, which is also used in excess compared to CO (3/1 ratio).

3.2 Tandem hydroformylation/asymmetric organocatalyzed transformations

In the past decade asymmetric organocatalysis has emerged as one of the main tools of enantioselevctive synthesis. Multiple reactions are catalyzed by organocatalysts of various structures and modes of action [64-66]. For the cross aldol reaction enamine catalysis is of special interest and it has allowed direct and enantioselective cross-aldol coupling between two non-equivalent aldehydes using the chiral primary or secondary amines as the catalysts. L-proline, cheap and widely available aminoacid from natural feedstock showed to be particularly interesting catalyst for aldol reactions.

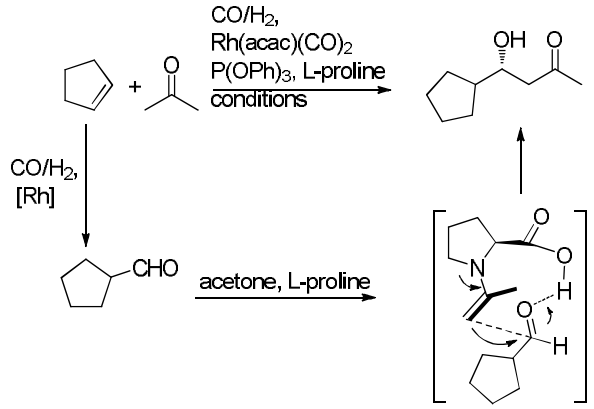
3.2.1 Tandem hydroformylation/Enantioselective cross aldol reactions

A difficult task in cross-aldol reactions is to avoid the formation of the homodimer aldols. The current solution to this problem is to keep the concentration of the donor aldehyde low by employing slow syringe pump additions.

An attractive alternative is to generate the aldehyde in a low stationary concentration in the course of a catalytic carbon-carbon bond forming reaction such as the hydroformylation of alkenes. This would result in a synthetically appealing domino hydroformylation/ organocatalytic aldol addition which starting from alkene feedstock would furnish enantioenriched aldolates in a one-pot operation.

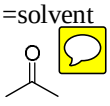
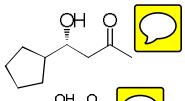
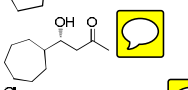
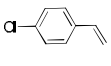
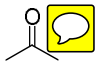
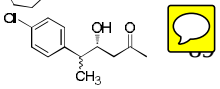
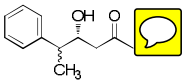
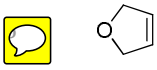
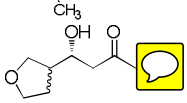
Eilbracht [67] and Breit [68] groups almost simultaneously reported on the cross aldol reaction under hydroformylation conditions. Both authors used L-proline as the organocatalyst of choice.
Eilbracht et al. used cyclic olefins to avoid regioselectivity issues of the hydroformylation reaction. Acetone was used as the solvent and as the donor component in the cross aldol reaction (Scheme 13). Mild conditions for the hydroformylation were developed in order to avoid enantioselectivity issues as well as the aldol condensation at higher temperatures (See Table 3 for conditions).

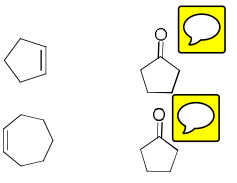
Scheme13. Tandem Hydroformylation/Organocatalyzed Enantioselective aldol reaction



Optimized, very mild reaction conditions were applied to different electrophile precursors (cyclic olefins). Good yields with enantioselectivities ranging from 71-96% ee and diastereoselectivities of up to 1/2.7 were achieved (Table 3).

Table 3. Scope Tandem hydroformylation/enantioselective aldol reaction

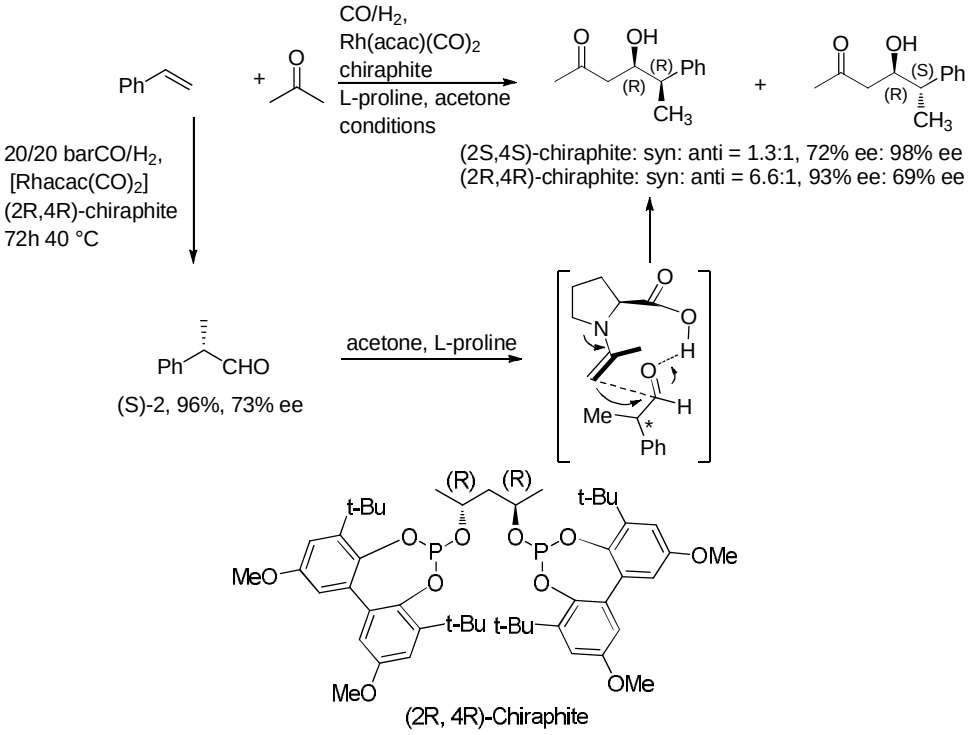
Entry	Substrate	Ketone =solvent	product	Yield [%][c]	syn:anti[d]	ee [%][e] syn/anti
1				76	/	75
2				47	/	89
3				89	1.5 : 1	72/99
4				83	1.5 : 1	72/99
				71	1 : 1	71/71

6		59	1 : 2.7	95[f] /96
7		76	1 : 1.9	83/ 85

0.5 mol% Rh(acac)(CO)2, 20/20 bar CO/H_2, 2 mol%$P(OPh)_3$, 30 mol% l-proline, 40 °C, 72 h..

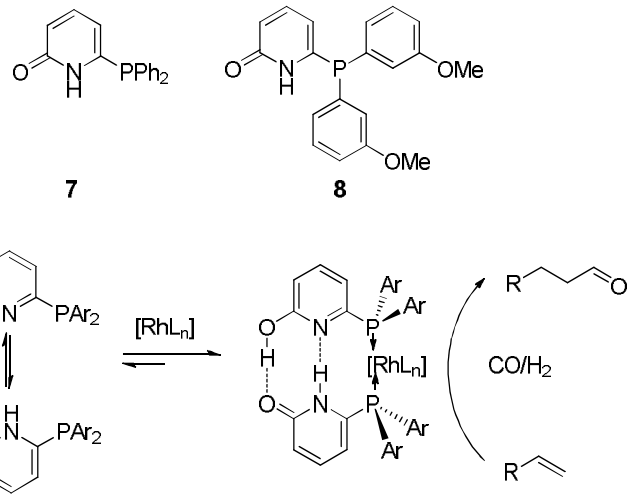
In the further development of this reaction same authors used a combination of chiral Rh catalyst with a chiral organocatalyst in a sequential hydroformylation/aldol reaction [69]. Chiral bisphospite ligand "Chiraphite" was chosen as a ligand of choice for the enantioselective hydroformylation of styrene. Up to 73% ee of 2-phenylpropanal were obtained in hydroformylation of Styrene at 40 °C. Diastereoselectivities of up to 6.6/1 in favor of *syn* isomer were obtained in cross aldol reaction which corresponds to the initial ratio of enantiomers in the hydroformylation step (73% ee = 86.5:13.5 = 6.6:1) (Scheme 14).

Scheme 14. Tandem enantioselective Hydroformylation/ asymmetric organocatalyzed cross aldol reaction



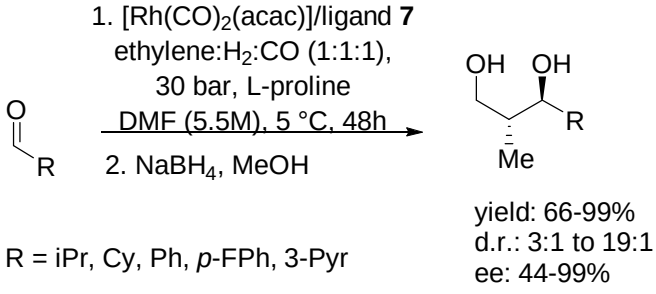
As already mentioned Breit group reported on tandem hydroformylation/Cross aldol reaction almost simultaneously with Eilbracht group. In order to achieve optimal diastereo- and enantioselectivity in the course of the organocatalytic aldol step selective hydroformylation catalysts, which can operate at temperatures as low as 0–5 °C was required. Thus, Rh(I) catalysts modified with either triphenylphosphine or the self assembling pyridone ligands **7** and **8** (Scheme 15) which have proved to furnish particularly reactive and regioselective hydroformylation catalysts at low temperatures were used.

Scheme 15. Structure and mode of action of the self-assembling ligands **7** (6-DDPon) and **8**



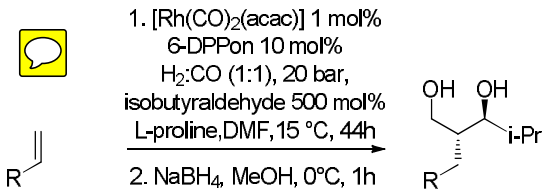
453

454 Ethylene gas was used as the precursor of the donor propionaldehyde in hydroformylation
455 reaction while the structural variation in the acceptor aldehyde component was studied
456 (Scheme 16).
457
458 Scheme 16. Tandem ethylene hydroformylation/enantioselective cross aldol reaction



459

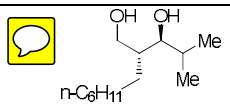
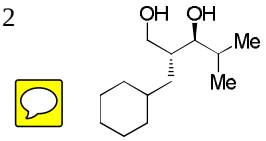
460
461 Extension to terminal alkene systems was explored too. Here regioselectivity of the
462 hydroformylation reaction had to be controlled. For this purpose rhodium/6-DPPon (**7**) was
463 employed as well [70, 71]. Thus, both 1-octene (Table 4, Entry 1) and vinylcyclohexane
464 (Table 4, Entry 2) could be employed to give the cross-aldol products in good diastereo- and
465 excellent enantioselectivity.
466
467 Table 4. Terminal alkene hydroformylation/enantioslective cross aldol reaction
468



469

470

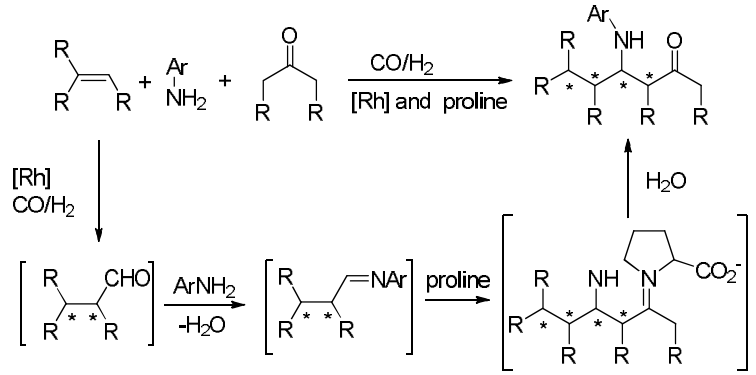
Entry	Product	Yield [%][a]	dr[b]	ee [%][c]

1		86	19:1	97
2		50	10:1	99

3.2.2 Tandem Hydroformylation/Enantioselective Mannich reaction

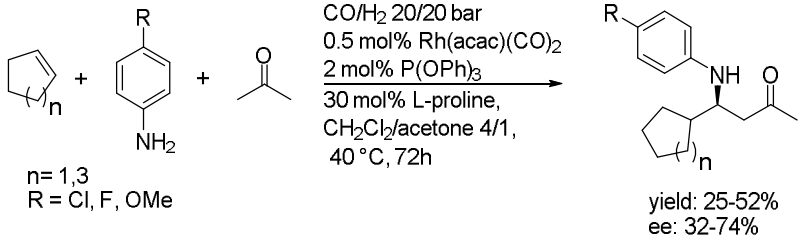
The already applied methodology for aldol reaction was further extended by Eilbracht et al. to Mannich reaction [72]. Sequential transformation involved hydroformylation of an alkene mediated by a triphenyl phosphite-modified Rh catalyst, condensation of aldehyde with primary amine present in the reaction mixture and L-proline-catalysed enantioselective Mannich reaction of the imine formed *in situ*, and ketone (Scheme 17). This process leads to the generation of up to four new adjacent stereogenic centers in the product.

Scheme 17. Tandem hydroformylation/enantioslective Mannich reaction



Cyclic olefins were used as substrates in order to avoid the regioselectivity problems of hydroformylation reactions. The hydroformylation reactions were performed using the previously reported protocol for cross aldol reactions (vide supra) Mannich products were obtained in up to 53% yield with moderate enantioselectivities of up to 74% (Scheme 18).

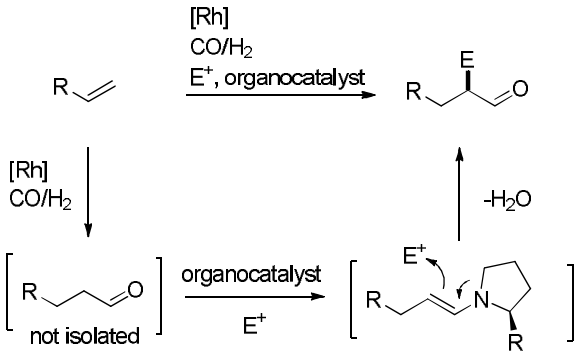
Scheme 18. Scope of tandem hydroformylation/enantioslective Mannich reaction



3.2.3 One-Pot Hydroformylation/organocatalyzed SN1 Alkylation

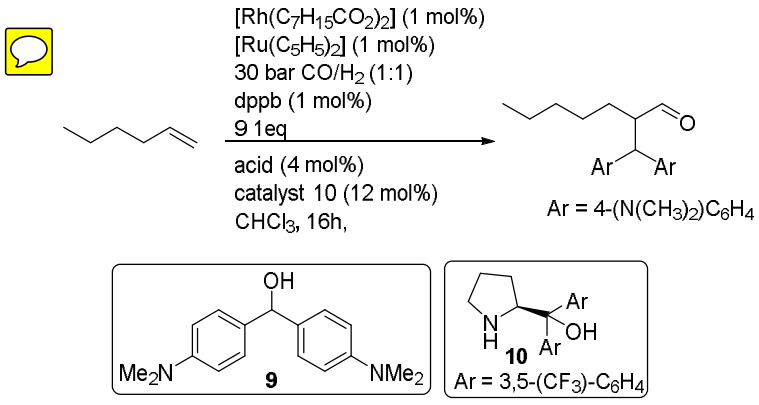
Christmann group reported on the tandem hydroformylation/enantioselective organocatalyzed alkylation reaction starting from simple olefins and using secondary alcohol **9** as the electrophile precursor (Scheme 19, Table 5) [73]. The reaction was run in the presence of DPPB as ligand for Rh, and in the presence of strong acid which is necessary for the *in situ* electrophile generation. Bidentate ligands, such as 1,4-bis(diphenylphosphino)butane (DPPB) or bis(2-diphenylphosphinophenyl) ether (DPEphos), showed a positive effect on the tandem reaction, whereas ligands with larger bite angles, such as biphephos and xanthphos, were inactive. The optimal rhodium-to-ligand ratio was determined to be 1:1 with good activity for the hydroformylation of 1-hexene.

Scheme 19. Tandem hydroformylation/enantioselective organocatalyzed alkylation reaction

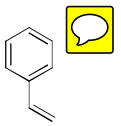
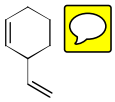
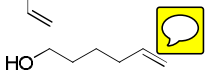
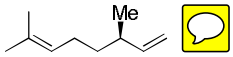
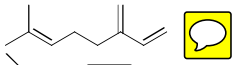


The Rh(II) octanoate dimer $[Rh(C_7H_{15}CO_2)_2]_2$ in combination with $[Ru(C_5H_5)_2]$ cocatalysts possessed the highest activity towards the product in the hydroformylation step. The cocatalyst not only enhanced the hydroformylation step, but also improved the conversion in the organocatalytic reaction. A number of linear, aromatic, and cyclic olefins underwent hydroformylation and subsequent alkylation with high enantioselectivities and yields. High ee's of up to 92% were realized using the Jorgensen–Hayashi diphenyl prolynol type organocatalyst **10** under the optimized conditions (Table 5).

Table 5. Scope of the tandem hydroformylation/organocatalyzed enantioselective alkylation



Entry	Substrate	t [h]	Yield [%]	ee [%]
1		16	64	90
2		16	58	91
3		16	62	92

4		16	43	93
5		16	85	93(93)(d.r.1:1)
6		16	83	83
7		16	76	98(80)(d.r.3:1)
8		16	n.r.	–
9		16	n.r.	–

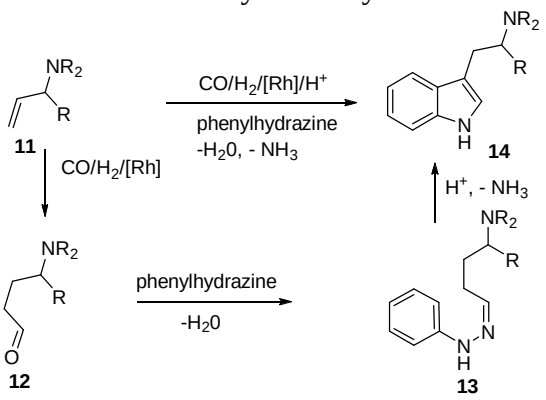
3.3 Tandem Hydroformylation/Fischer indole synthesis

The indole framework is one of the most frequently found structural motifs in natural products and pharmaceutically active compounds. Substituted indoles are referred to as "privileged structures" owing to their binding ability to many different types of receptors [74]. Due to these important properties new methods for indole synthesis and functionalization continue to attract attention [75, 76].

3.3.1 Tandem Hydroformylation/Fischer indole synthesis in the synthesis of indoles and carbazoles

Fischer indole synthesis is one of the most important approaches to indoles. In this reaction, aldehydes or ketones condense with arylhydrazines to arylhydrazones, which undergo a [3,3]-sigmatropic rearrangement to indoles in the presence of a Brønstedt resp. Lewis acid. Since under these conditions aldehydes tend towards side reactions, acetals or aminals are often used instead with *in situ* generation of the free aldehydes.
Direct tandem approach to indoles from olefins **11** includes three steps: the *in situ* generation of oxo aldehyde **12**, its conversion to aryl hydrazones **13**, and the [3,3]-sigmatropic rearrangement to the final product **14** (Scheme 20).

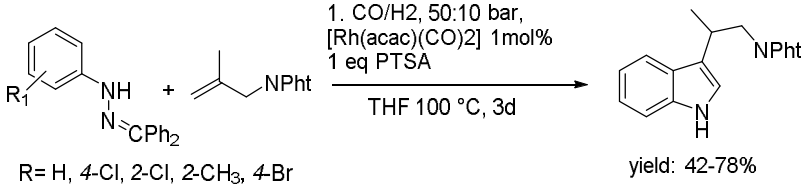
Scheme 20. General scheme of the tandem hydroformylation/Fischer indole synthesis



Indole derivatives with a tryptamine scaffold (3-aminoethyl indole) are particularly important compounds and many of these are known as synthetic medicines and physiologically active substances (serotonin, melatonin, psilocin,*etc.*). They were obtained starting from methallylic

amines in good yields using [Rh(acac)$(CO)_2$] as a catalyst and PTSA as an *in situ* present acid (Scheme 21) [77].

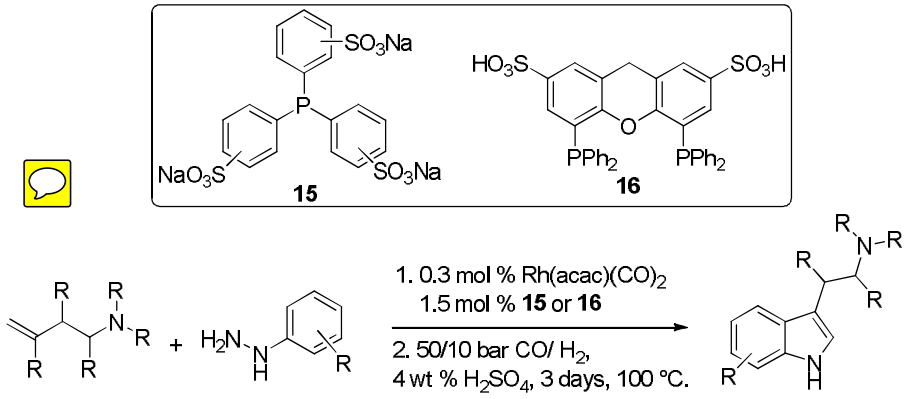
Scheme 21. Synthesis of tryptamines by Hydroformylation/Fischer Indole synthesis

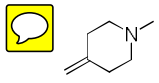
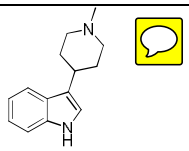


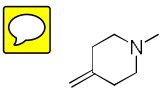
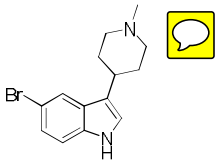
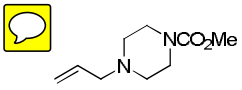
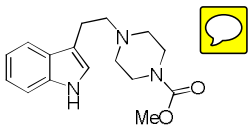
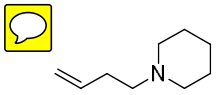
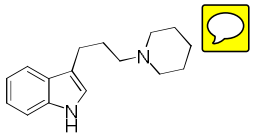
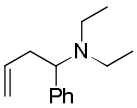
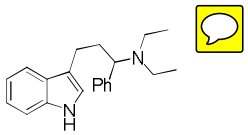
Using the same methodology branched tryptamines and homotryptamines possessing pharmacologically interesting properties have been synthesized as well [78].

Synthesis of branched tryptamines and homo tryptamines is possible in water as well. Solubility of the rhodium based hydroformylation catalyst in water and even in aqueous sulfuric acid was achieved by using sulphonated ligands such as TPPTS (**15**) or the analogous derivative **16** of XANTPHOS. As shown in Table 8, tandem hydroformylation/ Fischer indole synthesis in water gives in all cases excellent results. Regioselective tandem hydroformylation/Fischer indole synthesis in water is not limited to disubstituted terminal olefins as the substrates. Conversion of allylic and homoallylic amines also gives good to excellent yields of the desired tryptamine analogues (Table 6) [79].

Table 6. Synthesis of tryptamines and homotryptamines via Tandem Hydroformylation/Fischer indole synthesis in water



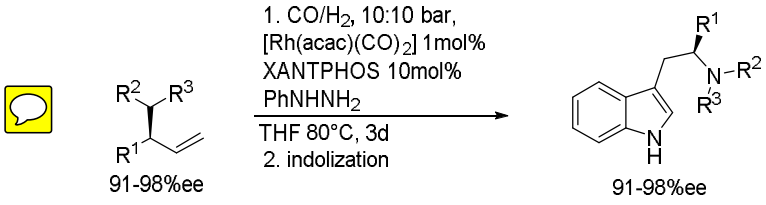
Entry	olefin	Hydrazine	product	Yield(%)
1		R = 4-H		80

2		R = 4-Br		96
3		R = 4-H		Quant
4		R = 4-H		50
5		R = 4-H		quant

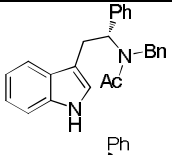
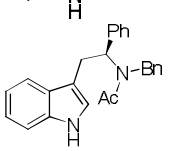
561

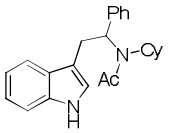
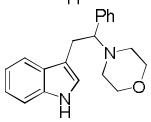
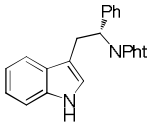
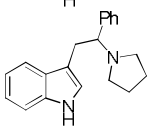
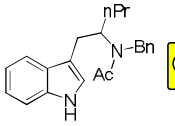
562 Further development of this methodology led to the synthesis of chiral tryptamines and
563 homologues. Combination of the enantioselective Ir catalyzed allylation chemistry for the
564 synthesis of required starting materials and the tandem hydroformylation/Fischer indole
565 synthesis sequence proved to be an efficient and highly diversity-oriented method [80]. The
566 tryptamines obtained from enantiomerically pure allylic amines reveal complete retention of
567 chirality although the stereocenter may epimerize during a tandem hydroformylation/Fischer
568 indolization via reversible double-bond isomerization or by the transition metal catalyst or
569 by the acid (Table 7).

570 Table 7. Some selected examples of Tandem hydroformylation/Fischer indole synthesis
571 starting with enantiopure allylic amines.



572

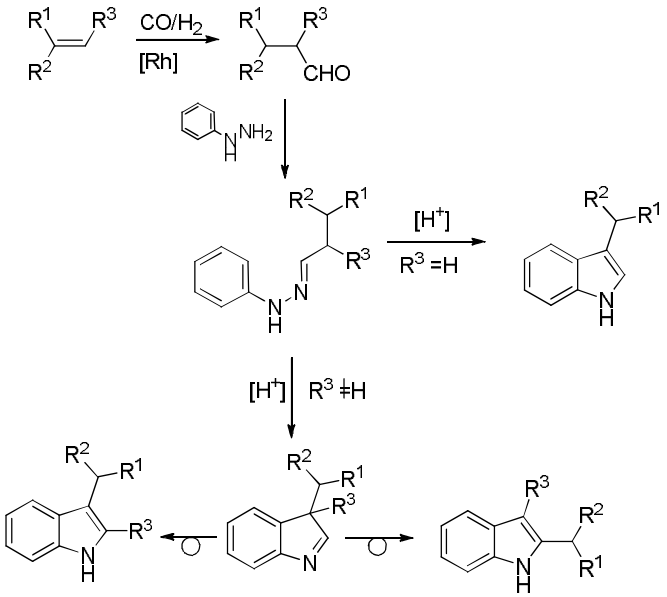
Entry	Substrate	Product	Yield,[a] ee%[b]
1	R1 = Ph, R2 = Ac, R3 = Bn		62%, (*R*) 92%ee
2	R1 = Ph, R2 = Ac, R3 = Bn		65%, (*S*) 97%ee

3	R1 = Ph, R2 = Ac, R3 = Cy			45%,
4	R1 = Ph, R2 = R3 = morpholine			52%, 97% ee
5	R1 = Ph, R2 = R3 = pht			67%, (*R*)
6	R1 = Ph, R2 = R3 = pyrrolidine			47%, 98%ee
7	R1 = nPr, R2 = Ac, R3 = Bn			76%, 91% ee

573

574 All described cases so far were dealing with terminal olefins giving rise to exclusivelly 3-
575 substituted indoles. However when internal or cyclic olefins are used , 2,3 disubstited indoles
576 or carbazoles (in the case of cyclic olefins) are obtained (Scheme 22) [81].

577 Scheme 22. Tandem hydroformylation/Fischer indole synthesis with internal olefins
578

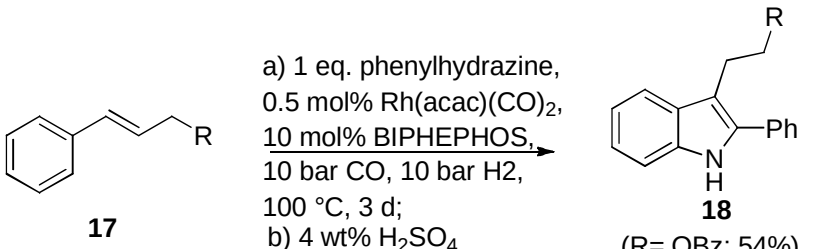


579

580

581 One representative example is shown in scheme 23. Unsymmetrical styrene **17** was submitted
582 to standard reaction conditions to give product **18** of exclusive Ph group migration, i.e. the
583 group which is better in stabilizing positive charge migrates faster (In this case Ph is faster
584 than alkyl group).
585

586 Scheme 23. Tandem reaction with unsymmetrical styrenes

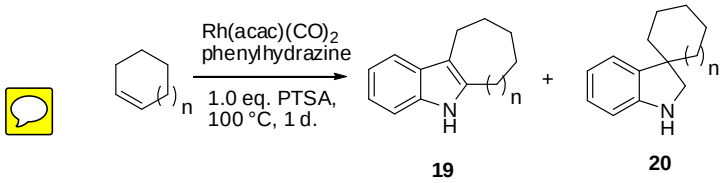


587

588

589 In the case of pentene it was observed that regardless of ratio of syngas carbazole product **19**
590 is obtained (Table 8, entries 1 and 2) however, in the case of six membered or higher cyclic
591 olefins it was observed that when higher partial pressure of hydrogen was used it was
592 possible to hydrogenate the spiro imino intermediate and isolate **20** in very good yield (Table
593 8, Entries 3 and 4). Substances of this type had not been observed with acyclic olefins,
594 presumably due to rapid rearrangements of the substituents at the quaternary centre. With
595 cyclic substrates it is clear that the rearrangement rate is influenced by the ring size.

596 Table 8. Hydroformylation/Fischer indole synthesis of cyclic olefins



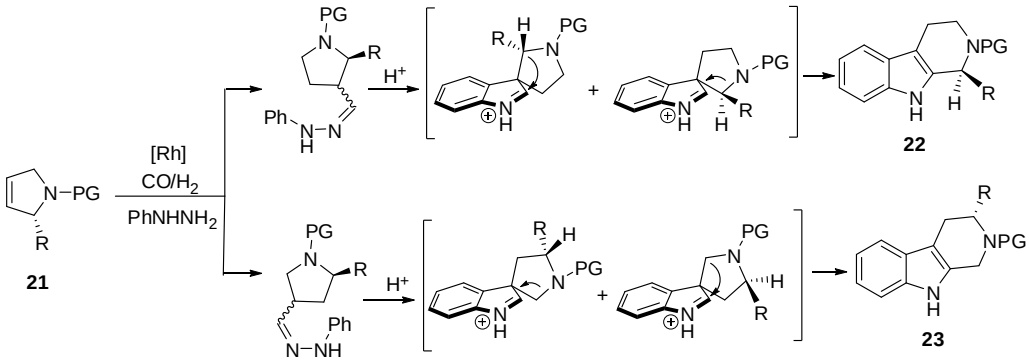
597

Entry	n	CO (bar)	H_2 (bar)	**19** (%)	**20** (%)
1	0	50	20	98	-
2	0	20	50	95	-
3	2	50	20	60	11
4	2	20	50	0	59

598

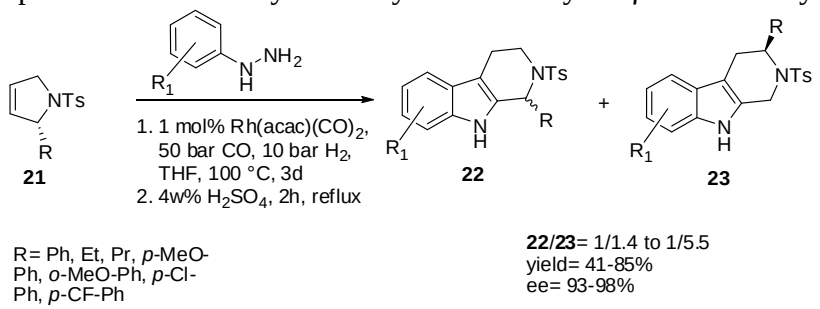
599 **3.3.2 Hydroformylation/ tetrahydro-β-carboline synthesis**
600
601 Among the indoles with an annelated heterocycle a very large and interesting group of
602 biologically active compounds are the tetrahydro-β-carbolines, which possess an additional
603 nitrogen atom in the third ring. Starting from 2-substituted 2,5-dihydropyrroles **21** which
604 were obtained via Ir catalyzed allylic amination/ring closing metathesis sequence and
605 following the stepwise protocol for hydroformylation/Fischer indole synthesis variety of
606 substituted chiral THBCs was synthesized (Scheme 24) [82].
607
608 Scheme 24. Mechanism of rearrangement of 3,3-spiroindoleninium cations in the synthesis

of tetrahydro-β-carbolines



In all cases good overall yields were obtained with clear preference for the formation of 5-subsituted THBCs **23**. 3-substituted carbolines **22** were isolated as racemates while 5-substituted retained enantiopurity of starting material (Scheme 25). The racemization 3-substituted carbolines appears to be the post rearrangement event caused by the acid present in the reaction mixture.

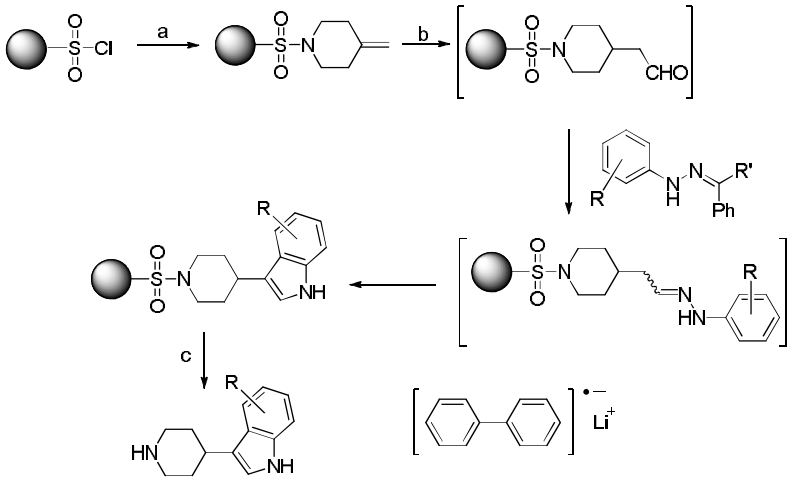
Scheme 25. Scope of the Tandem Hydroformylation/tetrahydro-β-carboline synthesis



3.3.3 Tandem Hydroformylation/Fischer Indole synthesis on Solid Phase

Synthesis on the solid phase was the next logical step in the development of the tandem Hydroformylation/Fischer Indole synthesis reaction [83]. Polystyrene sulfonyl chloride was used as an inexpensive linker resin. Secondary aminoolefins were attached to the resin in the first step and submitted to tandem reaction in the presence of hydrazine and acid (PTSA). Formed Indoles were cleaved from the resin under electron-transfer conditions (Scheme 26).

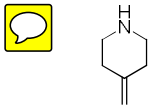
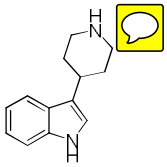
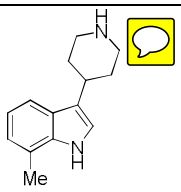
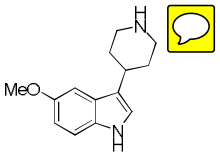
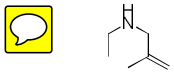
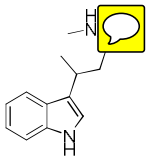
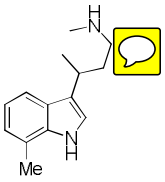
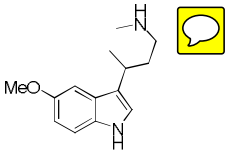
Scheme 26. Immobilization of olefins and domino hydroformylation/ indole synthesis followed by radical-anion-mediated cleavage



a) 2a,Py/THF 1:1, RT, overnight; b) 20 mol% [Rh(acac)(CO)$_2$], 50 bar CO, 10 bar H_2, 4a, PTSA, THF, 80°C, 2 d; c) 10 equiv **X** (1m in THF), THF, 0 °C, 2 h. Py=pyridine, THF=tetrahydrofuran, acac=acetylacetonate, PTSA=para-toluenesulfonic acid.

The orthogonality of this linker resin allowed the synthesis of a small library of novel tryptamines. After cleavage from the resin desired tryptamines were obtained in high purities. Reaction was run using variously substituted hydrazines as the nucleophilic comopnents in the reaction (Table 9).

Table 9. Yields and purities [%] in the synthesis of tryptamine and homotryptamine derivatives on solid phase

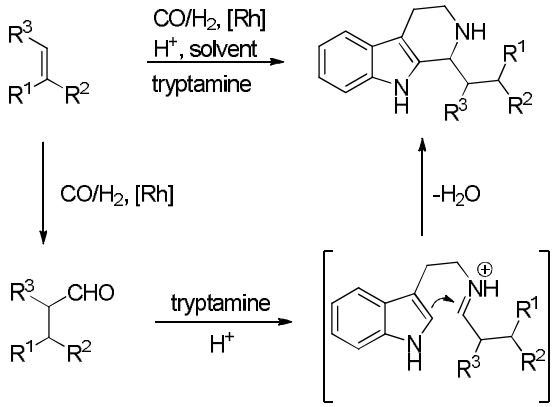
olefin	Products		
	R=H R'=Ph	R=o-Me R'=Ph	R=p-Ome R'=H
	 36 (96/88)	 27 (98/89)	 38 (93/75)
	 34 (73/85)	 36 (84/88)	 21 (70/83)

3.4 Tandem Hydroformylation/Pictet-Spengler reaction

Another approach towards substituted tetrahydro-β-carbolines involved Tandem hydroformylation/Pictet-Spengler reaction [84]. This tandem reaction allowed use of olefins as the precursors of the electrophylic component in the Pictet-Spengler reaction in

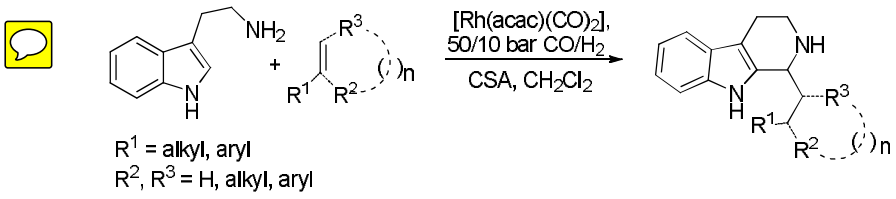
combination with tryptamine as nucleophile. In this reaction sequence the hydroformylation reaction in the presence of a rhodium catalyst is used to synthesize the aldehyde *in situ* from an olefin. In the presence of a β-arylethyl amine (and a Brønsted acid) this aldehyde is directly converted to a Schiff base which then subsequently cyclizes to form tetrahydro-*β*-carboline ring system (Scheme 27).

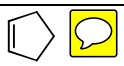
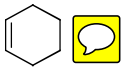
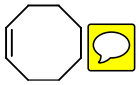
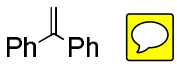
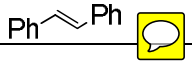
Scheme 27. Tandem Hydroformylation/Pictet Spengler reaction

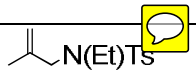
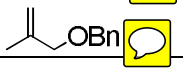


In all cases cyclic or 1,2 disubstituted olefins were used to avoid problems with regioselectivity of hydroformylation and in all cases good yields of desired products were obtained. High concentrations of the aldehyde are avoided due to the slower hydroformylation step, which prevents competitive aldehyde self-condensation reactions resulting in low yields. Thus some of the primary limitations of the conventional Pictet-Spengler reaction are avoided (Table 10).

Table 10. Tandem Hydroformylation/Pictet Spengler reaction



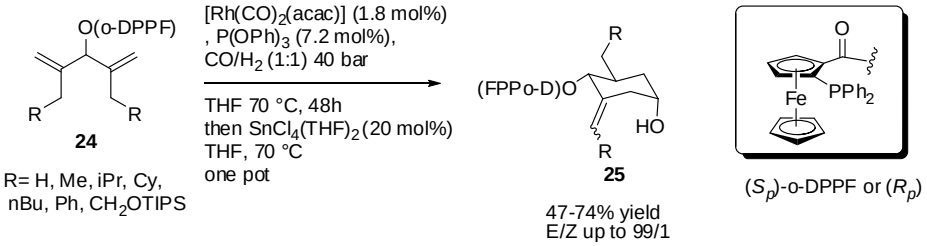
Entry	Substrate	T/°C	t/h	Yield (%)
1		80	72	65
2		110	80	46
3		80	68	68
4		80	72	59
5		110	72	64
6		110	72	49

7		110	72	74
8		110	72	82
9		110	72	51

3.5 Tandem Hydroformylation–Carbonyl ene cyclization reaction

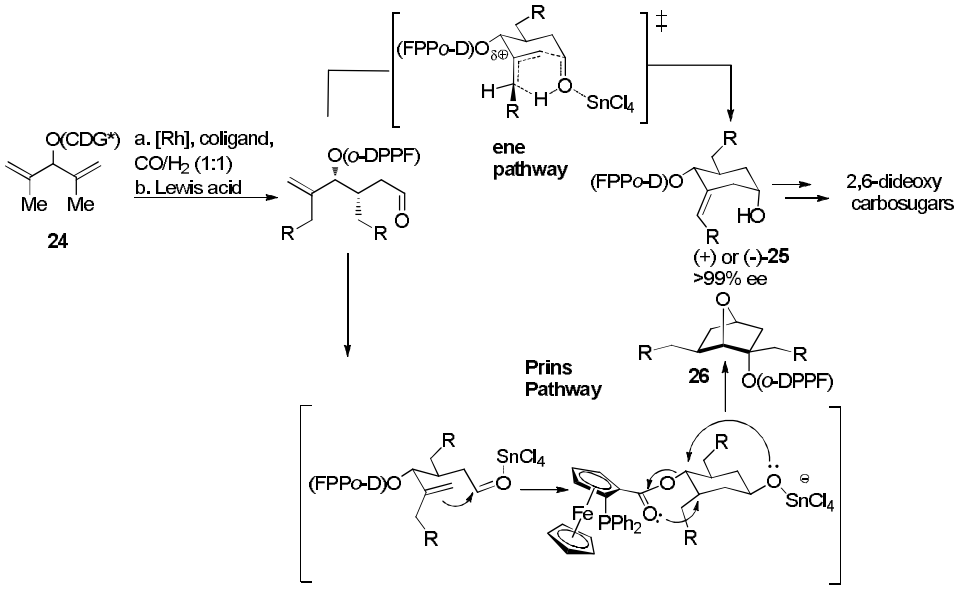
One-Pot Desymmetrizing Hydroformylation/Carbonyl Ene Cyclization Process was examined by the Breit group [85, 86]. The planar-chiral catalyst-directing group, *o*-(diphenylphosphanyl) ferrocenylcarbonyl (*o*-DPPF) moiety (Scheme 28), was attached to the symmetrical bis-2-propenyl-methanol. This group allowed for diastereotopic alkene group and face discrimination in the hydroformylation of **24** to furnish selectively the *syn*-aldehyde intermediate. Subsequent carbonyl ene cyclization and cleavage of the directing group in the same pot gave both optical antipodes of **25**, either starting from (*S*p)-*o*-DPPF ester or its (*R*p) enantiomer (Scheme 28).

Scheme 28. Tandem hydroformylation/carbonyl ene cyclization reaction



Starting from various dialkenyl-carbinol *o*-DPPF esters, a variety of functionalized alkylidene substituted cyclohexanols were synthesized in good yields and excelent E/Z selectivities
As a rationale for the formation of the bridged bicyclic ether **26** which was observed as a byproduct in the reactions, authors proposed a Prins-type attack to the activated aldehyde furnishing the cationic intermediate depicted in Scheme 29. Subsequent 1,2-migration of the *o*-DPPF ester through anchimeric assistance and ring closure by alkoxide nucleophilic displacement yields bicyclic ether **26**.

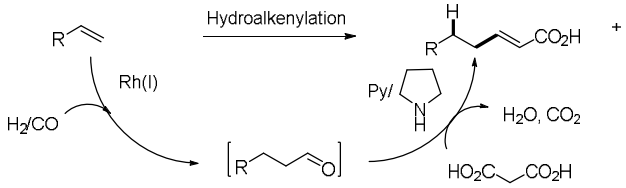
Scheme 29. Mechanism of Tandem Hydroformylation/carbonyl ene cyclization



3.6 **Hydroformylation/Decarboxylative Knoevenagel Reaction**

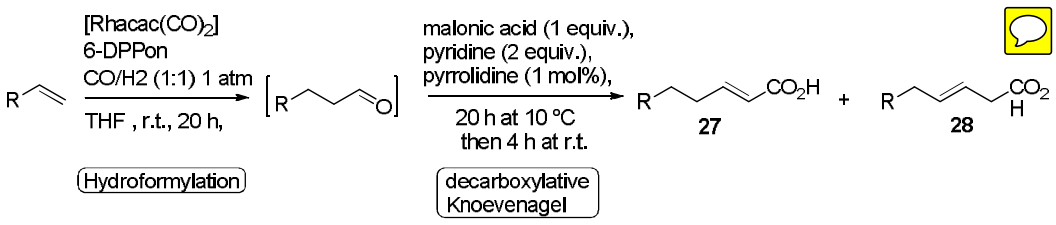
Breit group reported on the first one-pot hydroformylation/decarboxylative Knoevenagel reaction sequence, for the synthesis of α,β-unsaturated carboxylic acids **27** (Table 11) starting from olefins, a process combining an atom economic *in situ* aldehyde generation with a subsequent olefination process (Scheme 30) [87, 88].

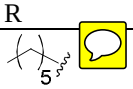
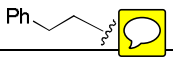
Scheme 30. Tandem Hydroformylation/decarboxylative Knoevenagel reaction

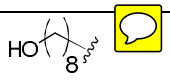
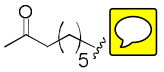
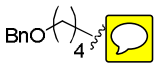
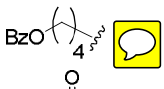
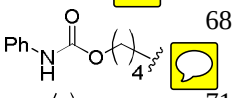
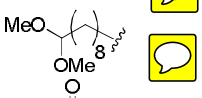
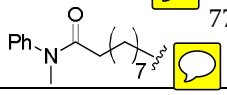


Optimized procedure is very reliable and seem to be general for terminal alkenes. Many functional groups including free alcohol functions as well as ketones, acetals, esters, amides and carbamates are tolerated (Table 11).

Table 11. One pot Hydroformylation/decarboxylative Knoevenagel reaction



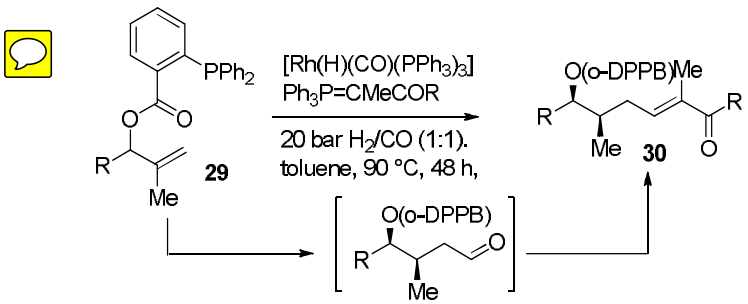
Entry	R	Yield [%]	**27:28**
1		77	98:2
2		78	97:3

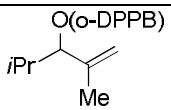
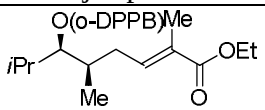
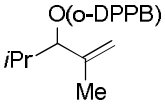
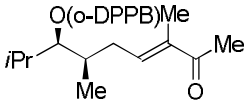
3		68	98:2
4		67	99:1
5		75	99:1
6		69	98:2
7		68	99:1
8		71	98:2
9		72	98:2
10		77	98:2

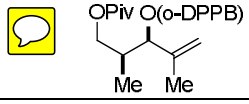
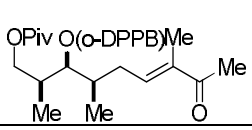
3.7 Tandem Hydroformylation/Wittig reaction

When o-DPPB esters **29** were subjected to hydroformylation conditions in the presence of the alkyl-substituted stabilized ylides the α,β-unsaturated carbonyl derivatives **30** were formed in good yield and diastereoselectivity (Table 12) [89]. A new carbon–carbon single bond as well as a new carbon–carbon double bond was formed concomitant with the installation of a new stereogenic center based on acyclic stereocontrol. The syn-diastereocontrol is the result of a directed hydroformylation step relying on the catalyst-directing ability of the o-DPPB group. The E-selectivity of the olefination step stems from the intrinsically high E-preference of stabilized phosphorus ylides.

Table 12. *o*-DPPB-directed diastereoselective domino hydroformylation–Wittig olefination reaction

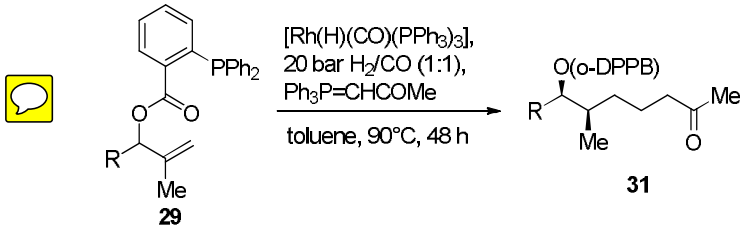


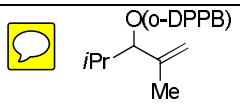
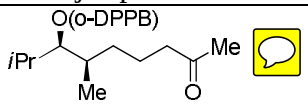
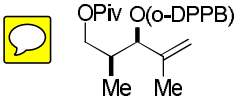
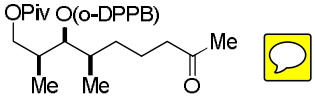
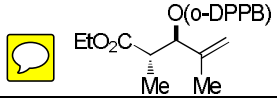
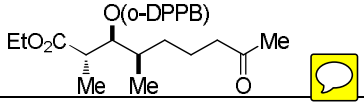
Entry	Substrate	Major product	Dr (syn/anti)	Yield%
1			96:4	75
2			93:7	78

3			92:8	60

However, employing the monosubstituted ylides furnished the saturated syn-1,6-oxygen functionalized ketones **31** in good yields and with high levels of acyclic stereocontrol. Due to less steric hindrance, the 1,2-disubstituted double bond of intermediate enone products undergoes hydrogenation reaction to give the saturated ketone (Table 13).

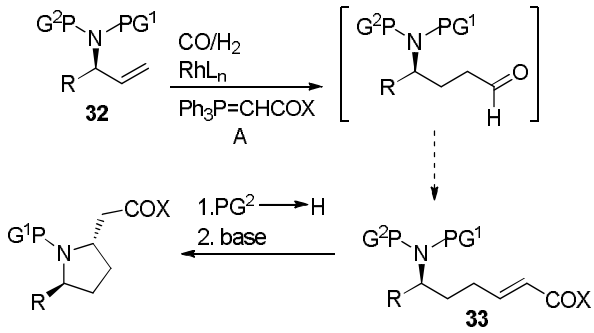
Table 13. *o*-DPPB-directed diastereoselective domino hydroformylation/Wittig olefination/hydrogenation reaction



Entry	Substrate	Major product	Dr (syn/anti)	Yield %[c]
1			94:6	70
2			96:4	68
3			94:6	60

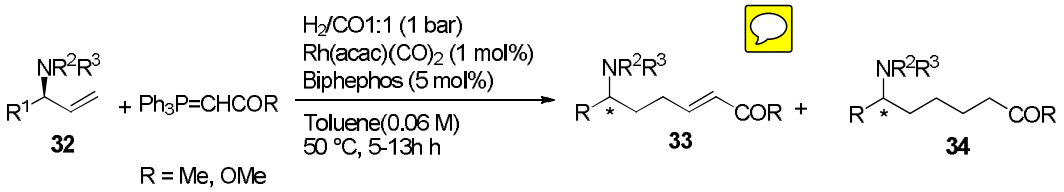
Helmchen group have found conditions allowing the direct preparation of α,β–unsaturated carbonyl compounds **33** under hydroformylation conditions starting from unsubstituted stabilized ylides and chiral allylic amines **32** (Scheme 31) [90]. The key for this selectivity were mild reaction conditions used. Reaction was run at 50 °C using BIPHEPHOS as the ligand. Full conversion of olefin to aldehyde could be achieved at atmospheric pressure of synthesis gas (H_2/CO 1:1) and in a short reaction time (5h). Enoates formed in this manner were used after deprotection and base catalyzed intramolecular cyclization for the synthesis of proline derivatives.

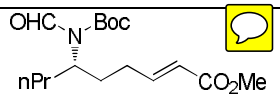
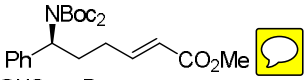
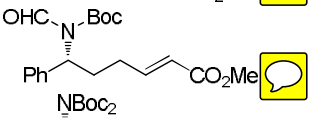
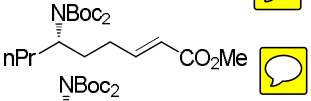
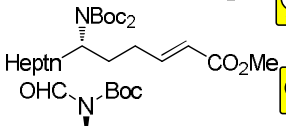
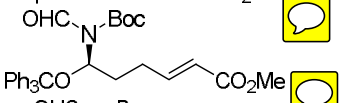
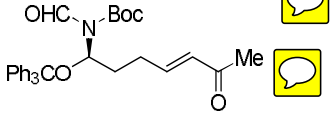
Scheme 31. Access to β-Proline Derivatives



The above very user-friendly reaction conditions were used to assess the scope of the domino reaction with a variety of chiral enantiopure allylamine derivatives and representative stabilized Wittig ylides (Table 14). The products **33**/**34** were obtained in 72–95% yield. Complete preservation of chiral information was observed in this reaction.

Table 14. Tandem Hydroformylation/Wittig olefination reaction

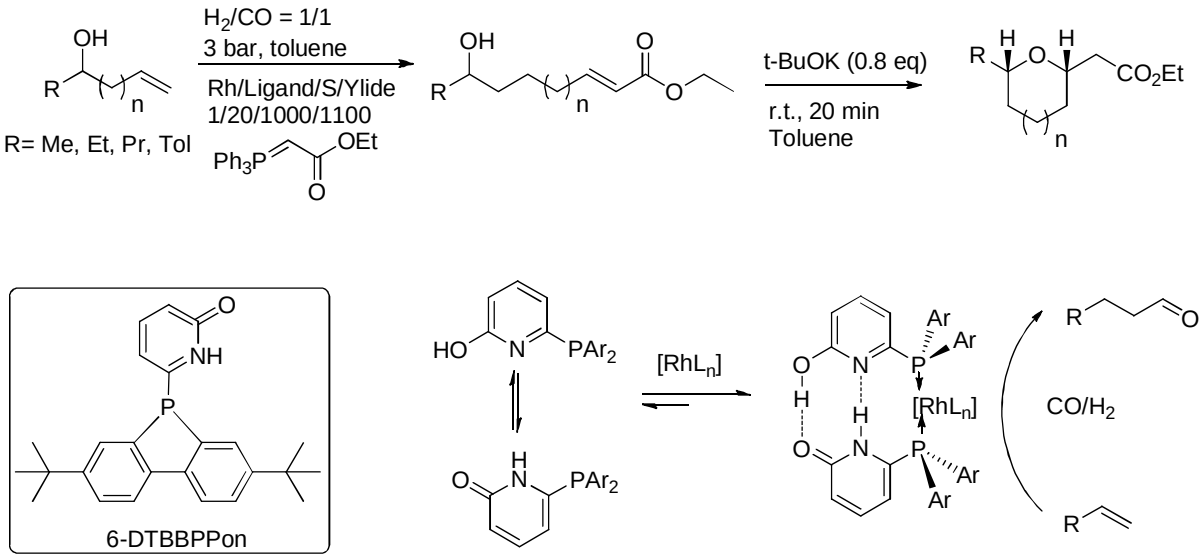


Entry	Product	Time [h]	Ratio **33**/**34**[a]	Ratio E/Z[a]	Yield (3)[b]
1		9	95:05	>91:09[d]	91%
2		5	95:05	>95:05	87%
3		12	94:06	>95:05	94%
4		6	97:03	>95:05	92%
5		5.5	98:02	>95:05	92%
6		5.5	91:09	>95:05	72%
7		13	81:19	>95:05	77%

[a] Determined by 1H NMR of the crude product. [b] Isolated yield.

To prevent hydrogenation of the enoates as a major side reaction Breit group developed new ligands based on the concept of self assembling. Several new ligands were designed and synthesized among which 6-DTBBPPon was identified as the best ligand in terms of activity, chemo- and regioselectivity (Scheme 32) [91].

Scheme 32. Tandem hydroformylation–Wittig olefination-Pyran synthesis and mode of action of selfassembling ligand 6-DTBBPPon

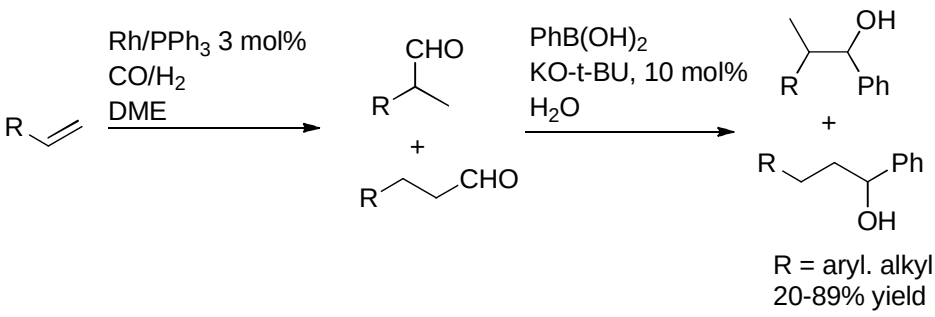


The obtained 7-hydroxy enoates could be cyclized by way of an oxa-Michael reaction to deliver the corresponding cis-pyrans in excellent yields (87-93%) and diastereoselectivities.

3.8 Miscellaneous Other Hydroformylations with Additional CC-Bond Formations

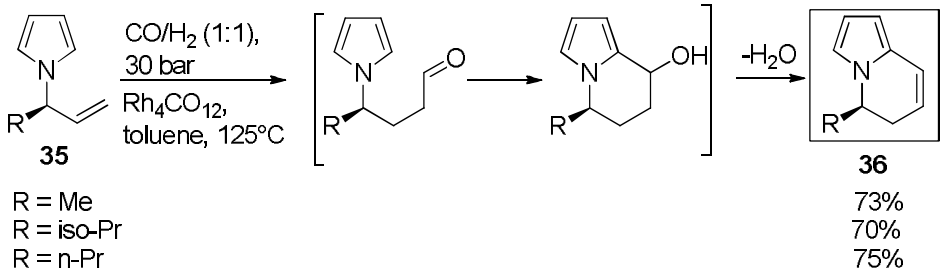
Tandem process using a single Rh catalyst to promote sequential hydroformylation/arylation reactions of aryl and alkyl olefins with arylboronic acids was investigated by Pereira group [92]. The rhodium/triphenylphosphine catalytic system was able to induce high conversions in the hydroformylation step (up to 99%) and regioselectivities for the branched aldehyde (up to 98%). This combined with high yields (up to 89%) for the subsequent arylation step to get final alcohols makes this process extremely useful. The scope of this multicatalytic synthetic methodology is demonstrated by the possibility of using different olefins and/or arylboronic acids containing electron- donating and electron-withdrawing groups. However, use of aliphatic boronic acids remains elusive (Scheme 33).

Scheme 33. Tandem Hydroformylation/Arylation Reaction with Boronic Acids



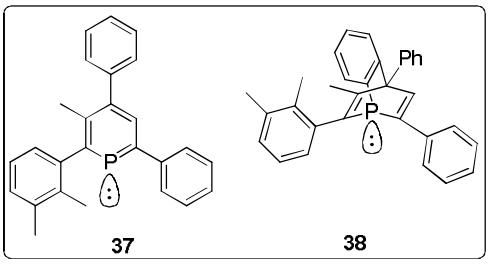
Tandem hydroformylation/cyclization reaction of enantioenriched N-allylpyrroles **35** provided new optically active 5-alkyl-5,6-dihydroindolizines **36** [93, 94]. Suitable experimental conditions avoiding racemization and enhancing the regioselectivity were found. Good yields of final products were obtained in all cases (Scheme 34).

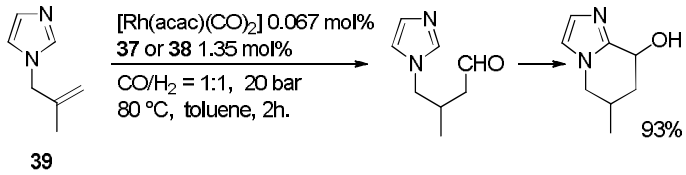
Scheme 34. Hydroformylation of (3R)-3-(pyrrol-1-yl)alk-1-enes **35**

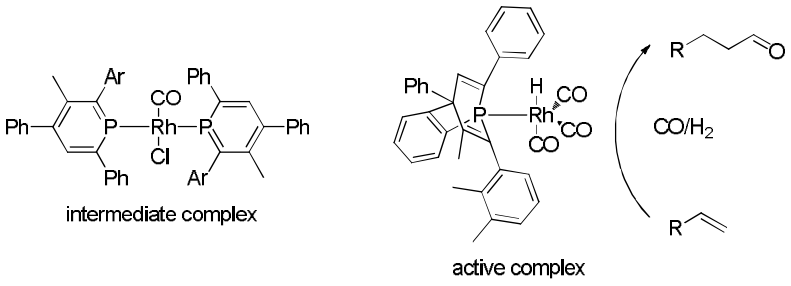


Tandem hydroformylation/cyclization reaction of N-methallylimidazoles was developed by Vogt et al [95]. Cyclized product was formed selectively in high yield by hydroformylation of N-(β-methallyl)imidazole **39** using a phosphabarrelene-modified Rh-catalyst and subsequent intramolecular cyclization (Scheme 35). These types of phosphorus ligands have previously been shown to be efficient ligands for the Rh-catalyzed hydroformylation of terminal and less reactive internal alkenes [96-103].

Scheme 35. Rh-catalyzed hydroformylation of N-methallylimidazoles and subsequent cyclization using Phosphinine **37** and phosphabarrelene **38**







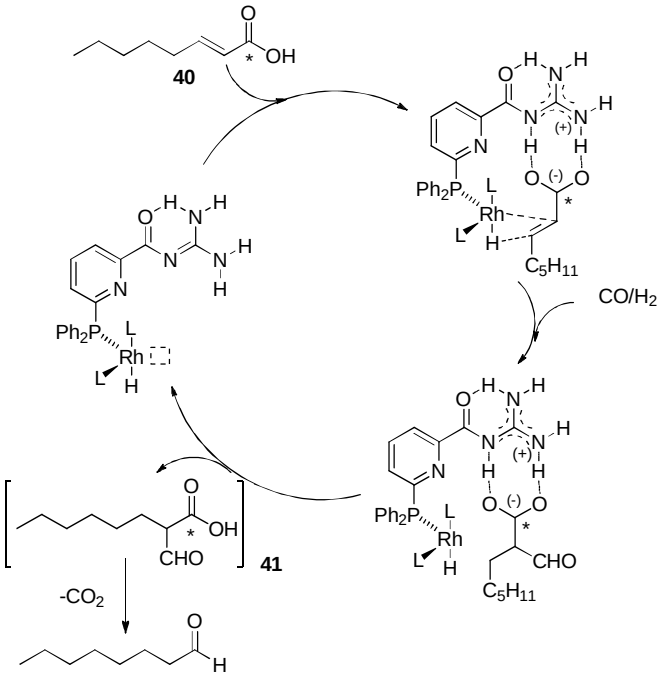
4. Tandem Hydroformylation/elimination reactions

4.1C-C bond cleavage reactions

4.1.1 Hydroformylation/decarboxylation of α,β-Unsaturated Carboxylic Acids

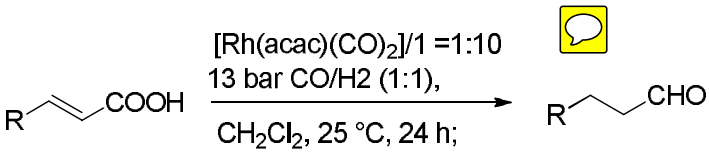
Breit group developed formal reduction of α,β-unsaturated acids to aldehydes [104] using supramolecular catalyst system (Rh cat/Lig 1, Scheme 36). Mechanism of reaction was proposed to consist of three consecutive steps:
a) binding of the substrate **40** to the ligand(s) of the rhodium complex (accompanied by substrate deprotonation), which activates the substrate;
b) α-selective hydroformylation within the supramolecular substrate–catalyst complex;
c) decarboxylation of α-formyl intermediate **41** to give aldehyde as the final product. Hence, the reaction proceeds as a decarboxylative hydroformylation.

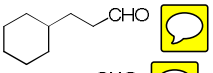
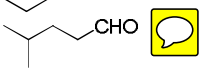
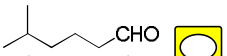
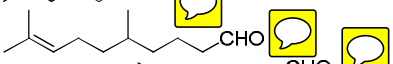
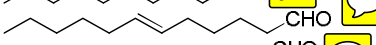
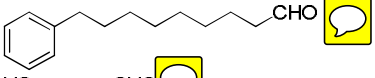
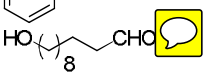
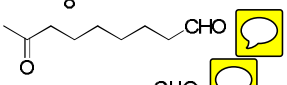
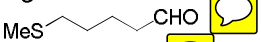
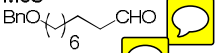
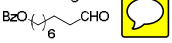
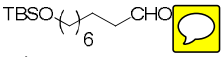
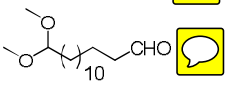
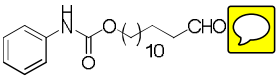
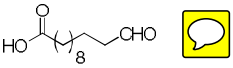
Scheme 36. The catalytic cycle proposed for decarboxylative hydroformylation catalyzed by $[Rh(acac)(CO)_2]$/1.



Reaction is quite general and good yields were obtained with substrates possesing olefins, alcohols, amides, acetals or carboxilic acids in side chain (Table 15).

Table 15. Reduction of α,β-unsaturated acids.



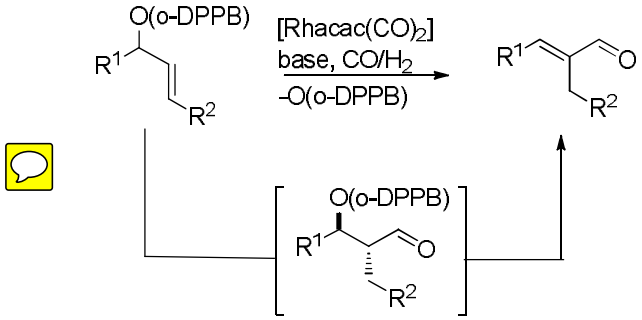
Entry	Product	Yield(%)
1		91
2		74
3		47
4		92
5		94
6		97
7		94
8		87
9		91
10		74
11		75
12		96
13		95
14		68
15		77
16		50

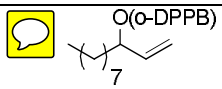
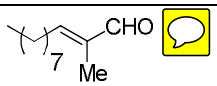
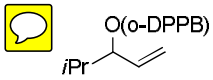
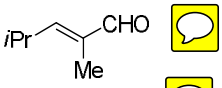
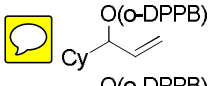
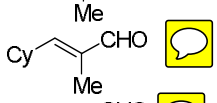
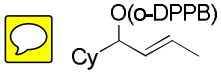
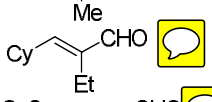
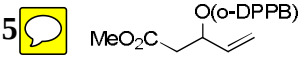
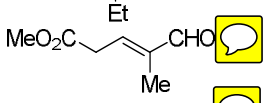
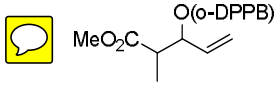
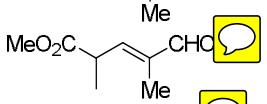
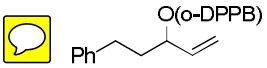
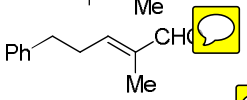
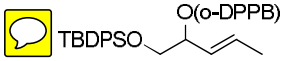
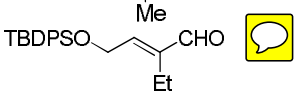
4.2 C-O cleavage reaction

4.2.1 Tandem Hydroformylation/β-elimination of *o*-DPPB esters

Practical synthesis of α,β-unsaturated aldehydes by a tandem-directed hydroformylation/β-elimination process of allylic *o*-DPPB esters was reported by Breit group [105]. The *o*-DPPB group served as an effective controller for regioselectivity of the hydroformylation towards the desired aldolate isomer, and was subsequently eliminated *in situ* by mild standard bases. The reaction is rather general for the preparation of 1,1-disubstituted and trisubstituted enals and is compatible with many functional groups (Table 16). Recovery of the *o*-DPPBA is possible either by chromatography or precipitation as the diethylammonium salt.

Table 16. Tandem hydroformylation/β-elimination reaction of allylic *o*-DPPB esters



Entry[a]	Substrate	Time (h)	Base (equiv)	Product	Yield(%)
1		31	Et_3N (1.1)		96
2		24	K_2CO_3 (0.1)		67
3		24	K_2CO_3 (0.1)		92
4		42	$HNEt_2$ (2.0)		86
5		24	K_2CO_3 (0.1)		78
6		24	Et_3N (1.1)		84
7		24	Et_3N (1.1)		92
8		48	Et_3N (5.0)		80

a $[Rh(CO)_2acac]$ (1.8 mol%), CO/H_2 (40 bar), THF (c = 0.1 M), tandem process, base present during hydroformylation;

5. Tandem Hydroformylation in the presence of N-nucleophiles

5.1 Dendrimer synthesis

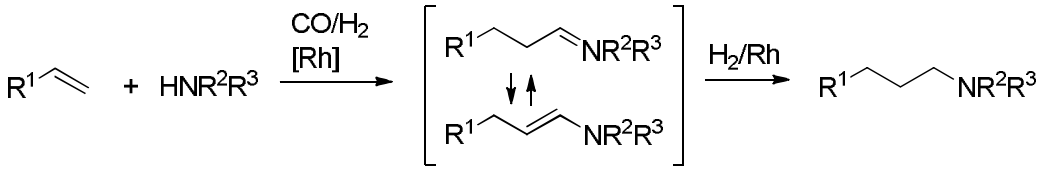
The interest in dendrimers, [106-108]which are ideally–perfect monodisperse macromolecules with a regular three-dimensional architecture, has grown exponentially over the last two decades. Due to the highly branched globular structure of dendrimers, they are attractive scaffolds for a wide variety of high-end applications, such as liquid crystals [109], diagnostics [110, 111], solar cells [112], sensors [113], gene-transfection agents [114, 115], drug-delivery systems [116], coating agents [117], additives in commodity plastics [118], and potential drugs [119]. Moreover, they have been successfully employed in a wide variety of catalytic reactions [120-123]as alternatives to insoluble solid-phase supports. They have also been found to be useful building blocks and carrier molecules that operate at nanoscales [124-126]. Most of the published examples of dendrimer synthesis to date use some kind of hydroaminomethylation reaction or at least reaction in the presence of *N*-nucleophile, for the

construction of dendritic unints , dendrons or entire dendrimers, hence, whole chapter of dendrimer synthesis will be placed in the hydroaminomethylation (N nucleophiles section) section.

5.1.1 Hydroaminomethylation (Hydroformylation/Reductive Amination) in the synthesis of dendrimers

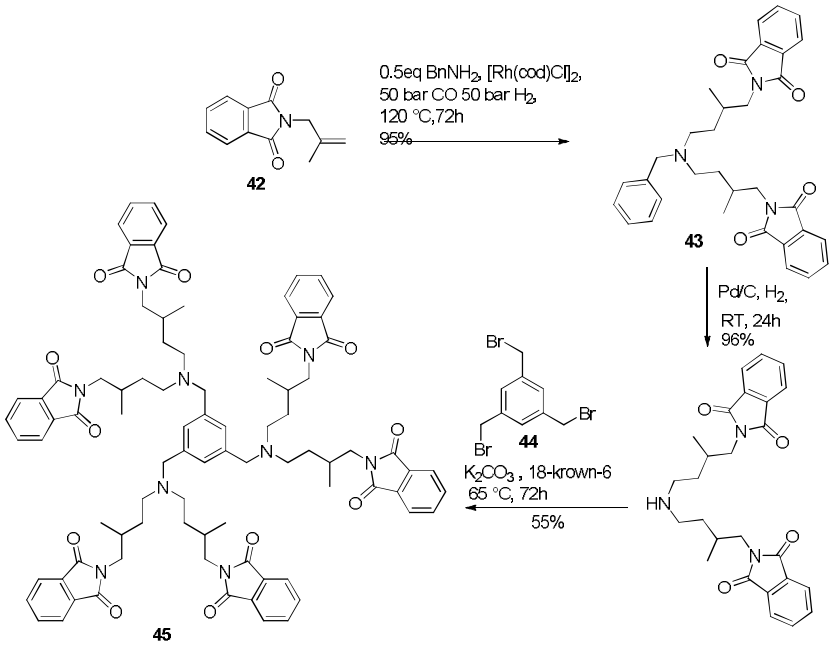
Recently hydroaminomethylation (Scheme 37), a rhodium catalyzed reaction sequence combining hydroformylation of olefins and reductive amination of the resulting aldehydes under the same conditions, has been used in the synthesis of linear and cyclic polyfunctionalized amines including polyamines and azamacroheterocycles [127-132].

Scheme 37. Hydroaminomethylation reaction principle



Eilbracht group applied this method to dendrimer synthesis offering access to new structural features. Dendrimer-type polyamines were synthesized via hidroaminomethylation procedure both using convergent and divergent strategies [133]. As building block the easily obtainable methallylphthalimide **42** was used as the olefinic reaction partner bearing a protected primary amino group which after deprotection provides the branching point for the next dendrimer generation. Following a convergent strategy, benzylamine is converted under hydroaminomethylation conditions with 2.0 equiv of methallylphthalimide **42** to afford the orthogonally protected triamine **43** in very good yields (Scheme 38). **43** is debenzylated under reductive conditions in nearly quantitative yield. The secondary amino group can then be attached to trihalide core **44** using general substitution conditions resulting in the polyamine dendrimer unit **45** in good yields (Scheme 38).

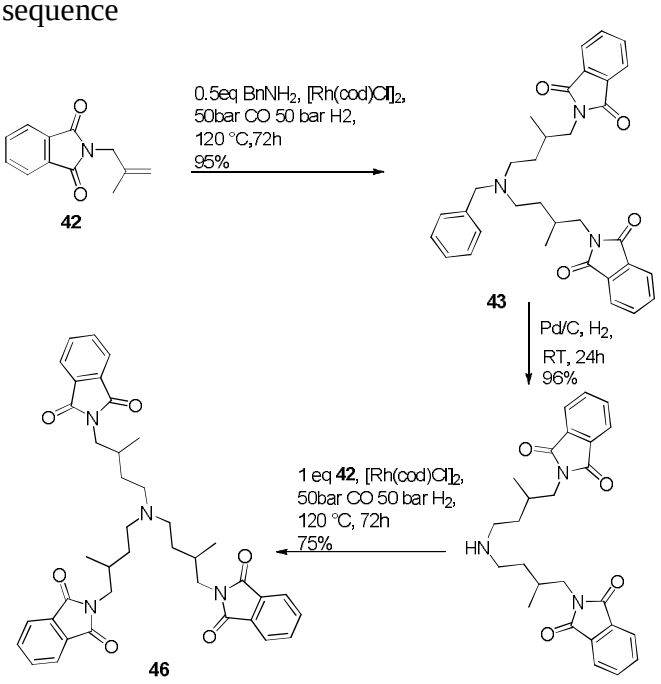
Scheme 38. Hydroaminomethylation in the synthesis of dendrimers



5.1.1.1 Hydroaminomethylation using Urea as an ammonia equivalent

In the first approach towards a synthesis of symmetric tertiary amines, benzylamine was used as an ammonia equivalent (Scheme 39) in order to circumvent the problems associated with direct alkylation of ammonia *via* reductive amination.

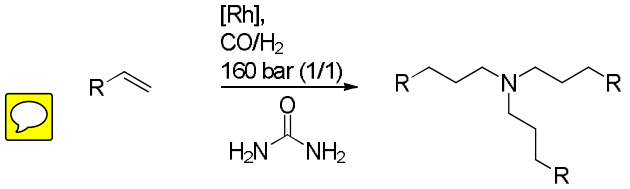
Scheme 39. Synthesis of polyamine **46** by the hydroaminomethylation–debenzylation sequence

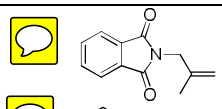
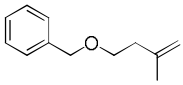


The rhodium catalyzed hydroaminomethylation reaction of olefins in the presence of an excess of ammonia only leads to secondary amines as the main product. If ammonia is not present in high concentrations in the reaction mixture, the corresponding alcohol is obtained

in large amounts [134-136]. However, urea was found to be good as an ammonia source since it forms ammonia upon hydrolysis under reaction conditions and simultaneously may act as a scavenger for aldehydes, protecting these against reduction thus allowing selective trisalkylation (Table 17) [137].

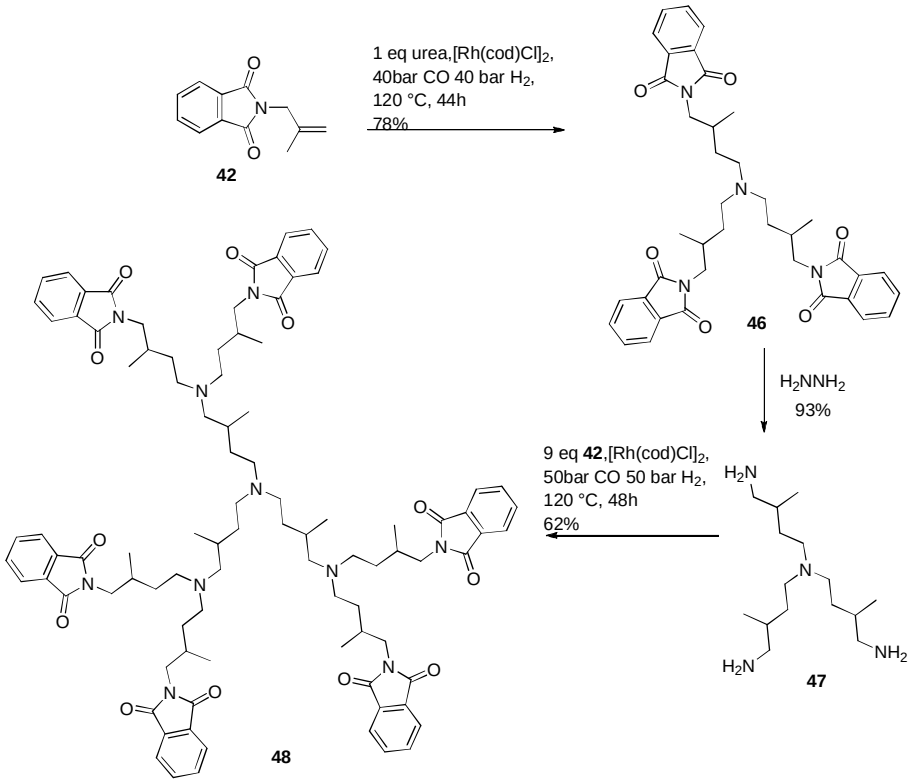
Table 17. Results of the synthesis of tertiary amines by hydroaminomethylation with urea



Entry	Olefin	T/°C	t/d	Yield (%)
1		120	2	78
2		120	3	94
3		120	2	85
4		100	2	77
5		100	2	74
6		100	2	67

Using this method the synthesis of **46** as described above (Scheme 39) can be shortened to a one step procedure yielding 78% (Scheme 40 and Table 17, Entry 1). Hydrazinolysis of **46** afforded the primary amine **47** in 93% yield which then was converted under typical hydroaminomethylation conditions yielding 62% of **48** (Scheme 40).

Scheme 40. Direct synthesis of polyamine **46** using urea and further conversion to polyamine **48**.

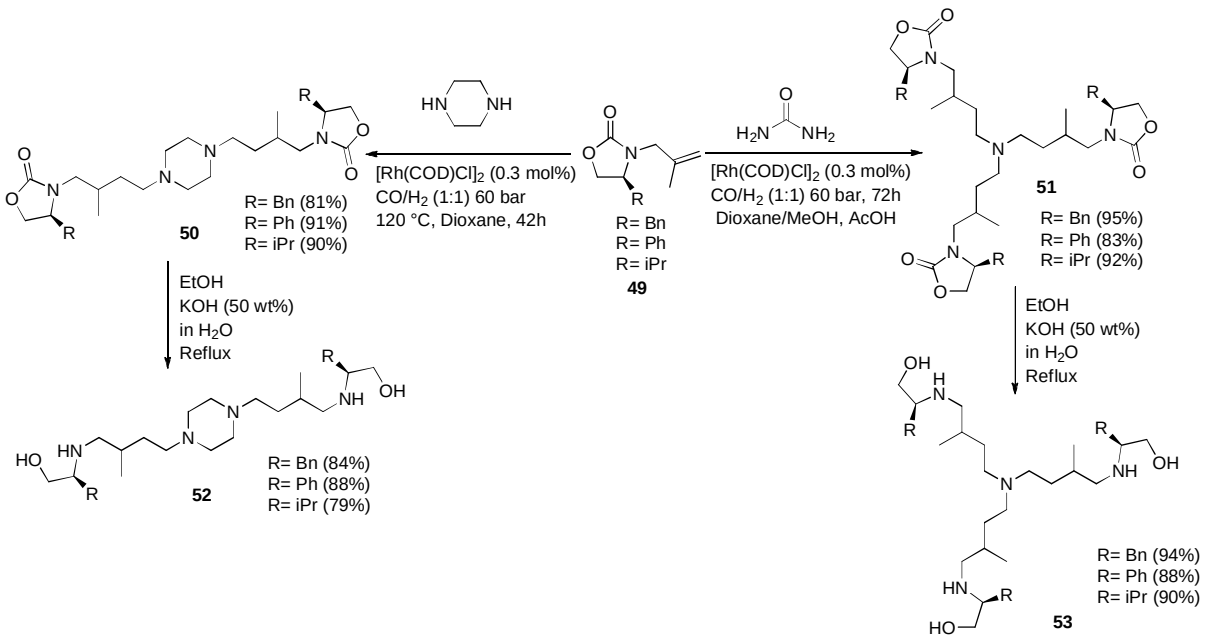


There are several more examples of application of hydroaminomethylation in construction of the polyamine/ polynitrile dendrimers through a convergent approach [138].

5.1.1.2 Chiral Dendritic Polyamino Alcohols

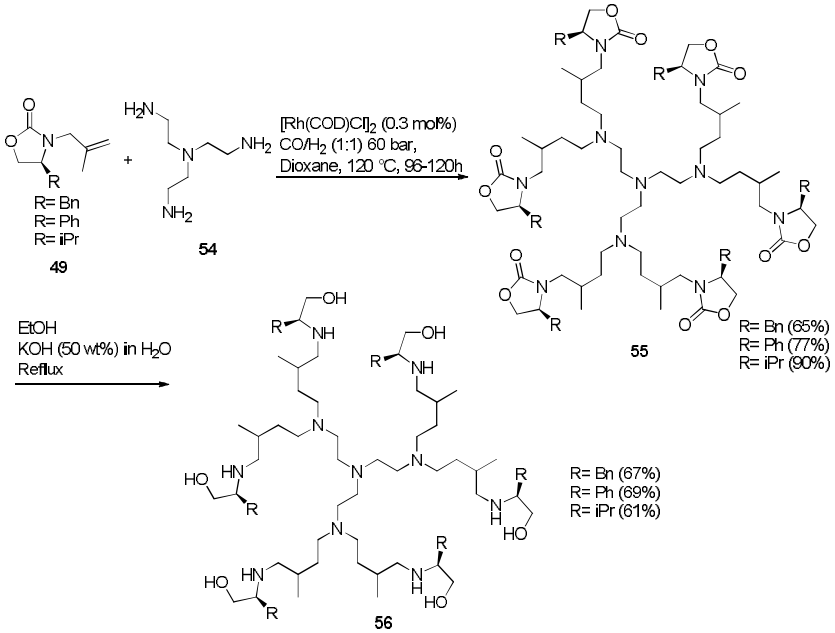
A new class of chiral polyamino alcohols (PAA) was synthesized via a two step hydroaminomethylation/hydrolysis procedure [139]. The chiral polyamines are obtained by hydroaminomethylation of *N*-olefinic oxazolidinones **49** with different amines in first step followed by hydrolysis of the resulting polyamines **50** or **51** to give the chiral PAA's **52** or **53** in the second step (Scheme 41).

Scheme 41. Synthesis of chiral PAA via hydroaminomethylation/hydrolysis



The tris(aminoethyl) amine **54** core molecule with three primary amine groups gives access to a 6-fold hydroaminomethylation that leads directly to higher Mw dendritic polyamines **55** in one step. The dendritic chiral PAAs **56** (Mw=1300–1400 gmol/1) were obtained in moderate to good yields upon hydrolysis (Scheme 42).

Scheme 42. Synthesis of dendritic chiral PAA via hydroaminomethylation/hydrolysis

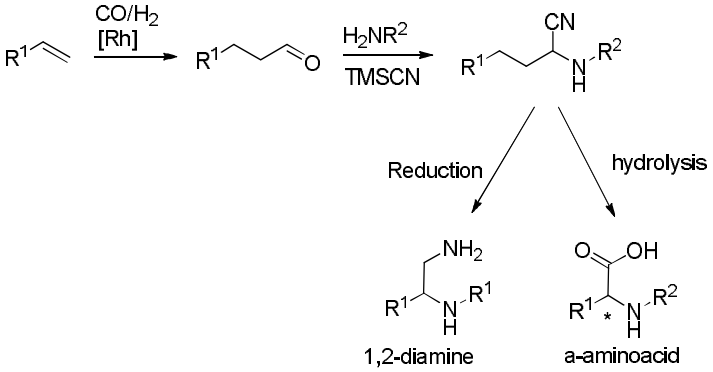


5.1.2 α-aminonitrile dendrimers via Strecker synthesis

One-pot hydroformylation/Strecker synthesis sequence was developed for the synthesis of racemic α-aminonitriles and dendritic polyamines with α-aminonitrile terminal groups [140]. This three component reaction consists of an initial hydroformylation of an olefin, which

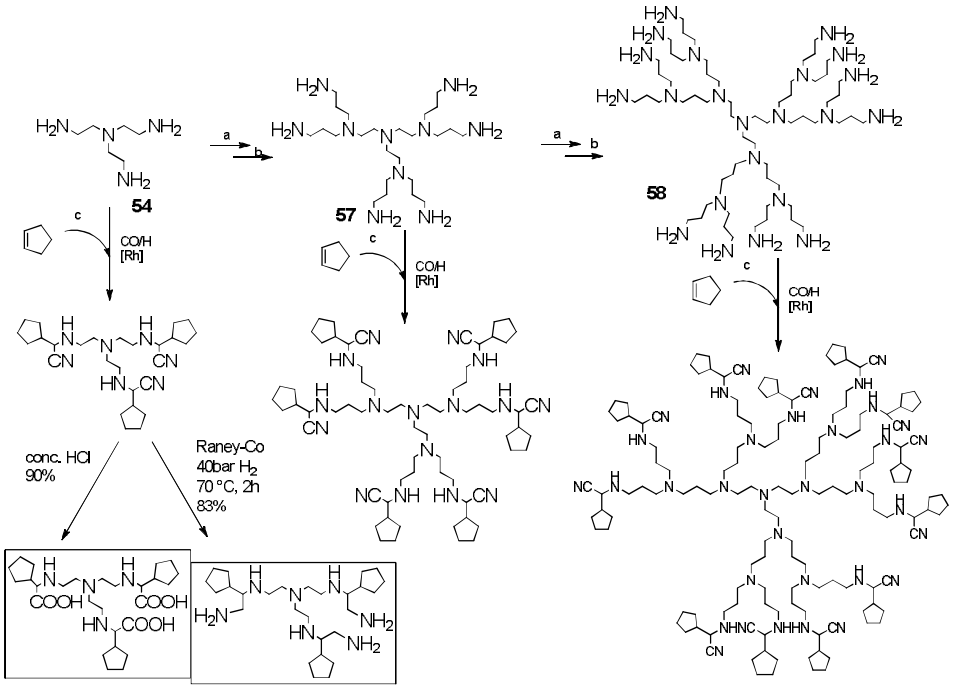
undergoes condensation with an amine to form an imine followed by the addition of CN^- to the C=N double bond of the imine to give α-aminonitriles (Scheme 43).

Scheme 43. Tandem Hydroformylation/Strecker synthesis



This methodology allowed functionalization of dendrimers (*e.g.* polyamines **54**, **57, 58**) and hyper branched polymers (*e.g.* polyallyl glycerol) to give corresponding dendritic structures with α-aminonitriles and/or amino acids in the outer shell in good to excellent yields. Higher generation poliamine cores were synthesized via Michael addition/reduction procedure (Scheme 44).

Scheme 44. Synthesis of α-aminonitrile dendrimers



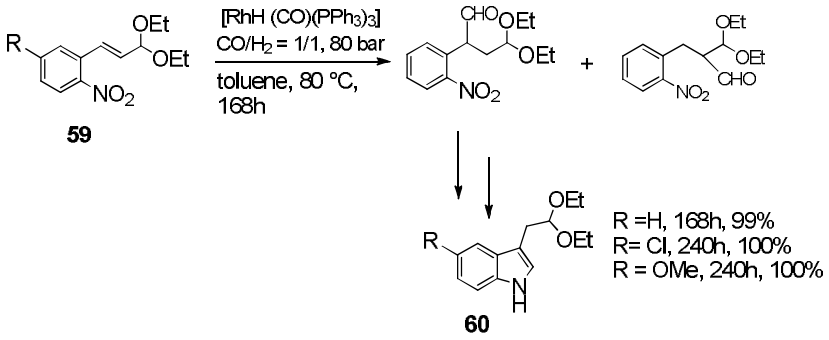
a)acrylonitrile, H_2O,3h reflux, b) Raney-Co (200 wt%) 40 bar H_2, 70 °C, 3h c) 1.$[Rh(cod)Cl]_2$, CO/H_2 (40/40bar), 48h, 100 °C 2. TMSCN, 12h, r.t.

5.2 *N*-heterocycles and alkaloid synthesis under hydroformylation conditions

5.2.1 Tandem hydroformylation/indolization of 2-nitrocinnamaldehydes

The synthesis of (1H-indol-3-yl)-acetaldehyde derivatives **60** was achieved via domino hydroformylation/indolization of 2-nitrocinnamaldehydes diethyl acetals **59**. This reaction sequence required efficient hydroformylation, reduction of the nitro group and intramolecular amino reduction followed by dehydration (Scheme 45) [141]. It was found that the best yield is obtained when [$RhH(CO)(PPh_3)_3$] was used as the catalyst. Hydroformylation is regioselective and gives almost exclusively desired isomer.

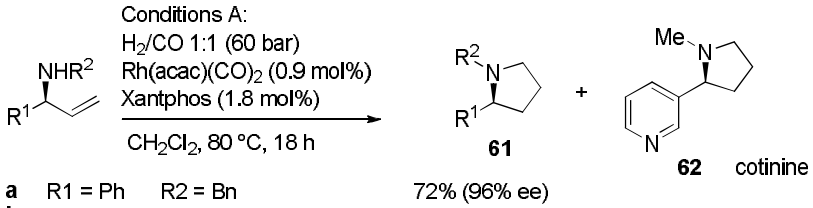
Scheme 45. Hydroformylation of 5-substituted-2-nitrocinnamaldehyde diethyl acetal



5.2.2 Tandem Hydroformylation/intramolecular hydroaminomethylation

2-Substituted pyrrolidines were synthesized starting from enantiopure branched allylamines by domino hydroformylation/intramolecular hydroaminomethylation reaction [142]. Desired products **61a–c** were obtained in 57–72% yield. With XANTPHOS as ligand the major product was the lactam cotinine **62d**, a tobacco alkaloid (Scheme 46).

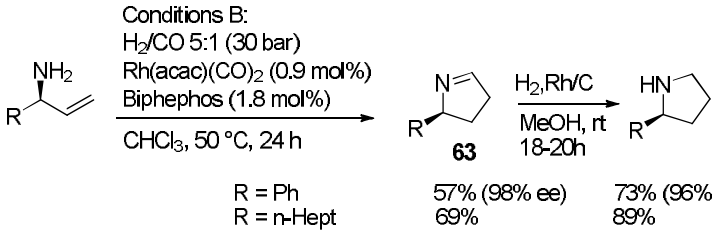
Scheme 46. Synthesis of 2-Substituted pyrrolidines



a	R1 = Ph	R2 = Bn	72% (96% ee)
b	R1 = Ph	R2 = CH2(4-MeOC6H4)	64% (98% ee)
c	R1 = 3-Py	R2 = CH2(4-MeOC6H4)	57% (98% ee)
d	R1 = 3-Py	R2 = Me	**61** (23%) + **62** (44%)

N-unprotected primary allylamines were subjected to the hydroformylation reaction as well (Scheme 47). Under the optimized conditions [Biphephos, 30 bar, H_2/CO (5:1), $CHCl_3$] the imines **63** were formed in good yield; reductive amination however did not occur.

Scheme 47. Hydroformylation–cyclization of primary allylamine

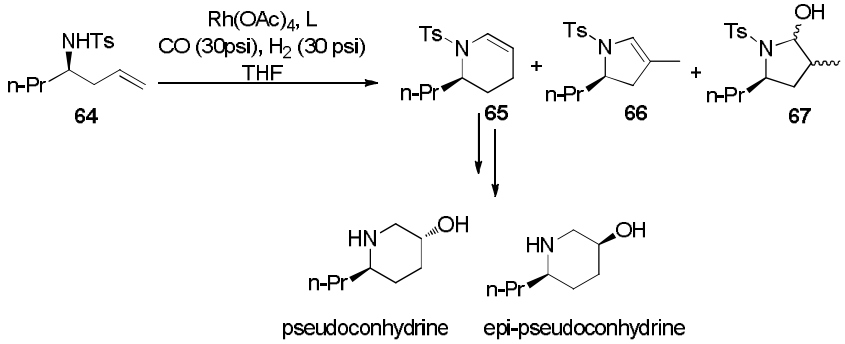


5.2.3 Tandem hydroformylation/cyclization sequence

Tandem hydroformylation/condensation chemistry, followed by oxidation of the resulting enamine derivative, was used to synthesize pseudoconhydrine, one of the alkaloids from hemlock (Conium maculatum) [143].

Hydroformylation of alkene **64** was carried out to give the product of linear hydroformylation, ene-sulfonamide **65**. While the linear product was always obtained in its dehydrated form as a cyclic ene-sulfonamide, the branched product was usually obtained as a mixture of dehydrated form **66** and the cyclic N,O-acetal **67**. On the other hand, use of the bulky bisphosphite BIPHEPHOS resulted in complete selectivity for the linear isomer **65**. Further transformations of **65** furnished pseudoconhidrine and epi-pseudoconhidrine (Scheme 48).

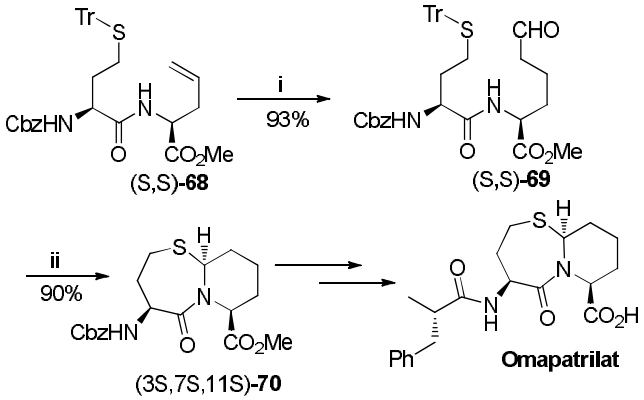
Scheme 48. Synthesis of pseudoconhidrine via tandem hydroformylation/cyclization sequence



5.2.4 Cyclohydrocarbonylation of dipeptides

Ojima et al reported the cyclohydrocarbonylation of dipeptides bearing a terminal olefin moiety catalyzed by Rh-BIPHEPHOS [144]. 1-Aza-6-thiabicyclo[5.4.0]undecane amino acid derivative (3*S*,7*S*,11*S*)-**70** was synthesized from *N*-Cbz-*S*-Tr-(*S*)-homo-Cys-(*S*)-(allyl)Gly-OMe [(*S*,*S*)-**69**] in 84% yield for two steps (Scheme 49). It is worth noting that this azabicyclo[5.4.0] framework is the core part of Omapatrilat, an effective ACE inhibitor developed by the Bristol-Myers Squibb company.

Scheme 49. Cyclohydrocarbonylation of (*S*,*S*)-**68**

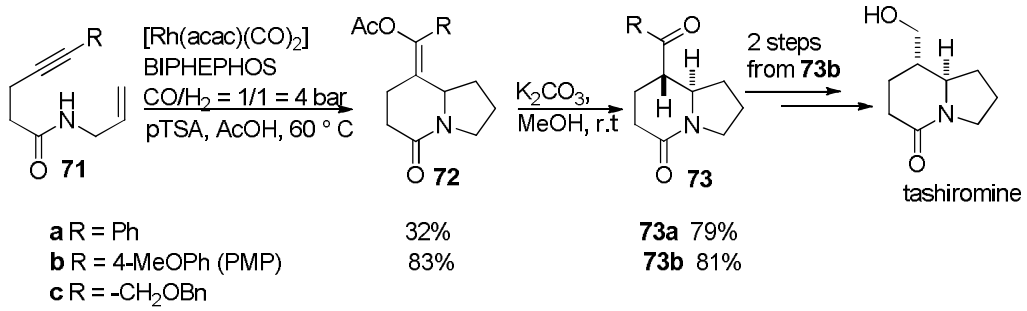


a Reagents and conditions: (i) $Rh(acac)(CO)_2$ (2 mol %), BIPHEPHOS (4 mol %), H_2 (2 atm), CO (2 atm), MeOH, 65 °C, 20 h; (ii) $MeSO_3H$ (1%), CH_2Cl_2, 30 °C, 1 h and then Et_3SiH (2 equiv) in TFA.

5.2.5 Alkyne-mediated domino hydroformylation/double cyclization

Alkyne-mediated domino hydroformylation/ double cyclization, has been developed for rapid preparation of indolizidine type alkaloids [145]. Treatment of amides **71** under the hydroformylation condition (Scheme 50) afforded a cyclized products **73a-c**. Electron donating group on the phenyl moiety enhances the nucleophilicity of the triple bond moiety. Thus, reaction of amide **71b**, bearing a para-methoxyphenyl group, was carried out to yield single E-enol acetate **72b** in 83% isolated yield. Tashiromine was synthesized in 2 steps from **73b** as the application of this methodology.

Scheme 50. Hydroformylation/cyclization reactions of amides **71a-c**



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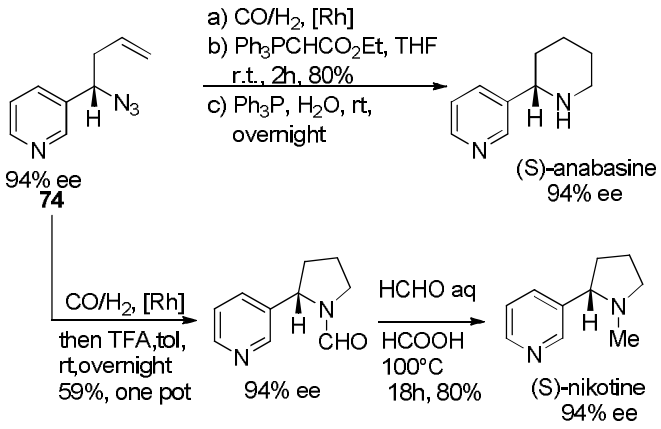
5.2.6 Hydroformylation of homoallylic azides

Hydroformylation of homoallylic azides combined with useful one-pot operations provided an expeditive access to pyrrolidine and piperidine alkaloids [146]. The chiral pyridinyl-homoallylazide **74** was recognized as an ideal substrate for a hydroformylative synthesis of two major alkaloids from *Nicotiana tabacum*, (*S*)-anabasine and (*S*)-nicotine via a One-Pot Hydroformylation/Hydrogenation and Hydroformylation/Schmidt Rearrangement sequences (Scheme 51). Rh/PPh_3 catalytic system has been successfully employed in this transformation.

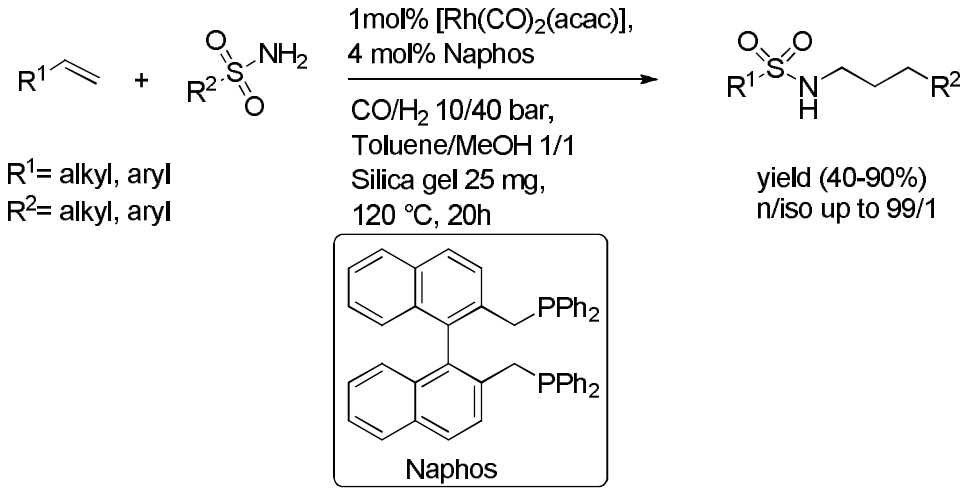
Scheme 51. Diversity Oriented Synthesis of (*S*)-Anabasine and (*S*)-Nicotine via a One-Pot Hydroformylation/Hydrogenation and Hydroformylation/Schmidt Rearrangement



5.3 Tandem hydroformylation/reductive sulphonamidation

An efficient and highly selective method for the synthesis of sulphonamides by a domino hydroformylation-reductive sulphonamidation reaction was developed [147]. Various olefins and sulphonamides were converted into the desired products in good yields and with excellent selectivities in the presence of a rhodium/Naphos catalyst. The weaker nucleophilicity of these nitrogen sources compared to that of amines impedes the condensation step with the aldehydes formed via hydroformylation, hence harsher conditions were required for condensation step to take place (120 °C, 20h reaction time). Under the optimized conditions various olefins were converted to N-substituted sulphonamides (Scheme 52).

Scheme 52. Domino hydroformylation/reductive sulphonamidation



6. Tandem hydroformylation-acetalization

Acetal formation under hydroformylation conditions may occur when the hydroformylation reaction is performed in the presence of alcohols or in alcohol solvents and can be used to modify the aldehyde unit for further synthetic purposes or for the synthesis of cyclic systems (5 and 6 membered) in the case of the intramolecular variant of the reaction. However, hemiacetals, acetals, or enol ethers might not always 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 [148-151]. 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.

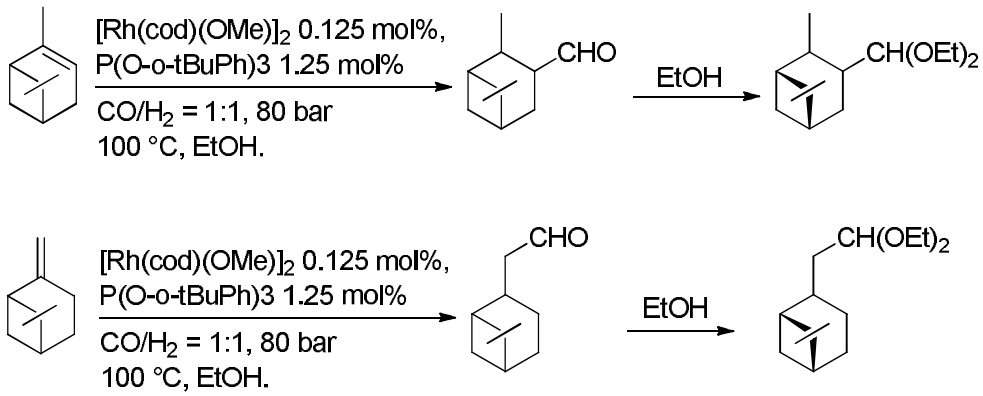
Various examples of direct acetal formation under hydroformylation conditions in the presence of alcohols are reported [152-156].

6.1 Intermolecular acetalization reaction

Recently study on reaction kinetics and reaction scope, and the mechanism of acetal formation in the absence of acidic co-catalysts has appeared [157]. Also the effects of different Rh precursors on the selectivity of acetals in tandem hydroformylation–acetalization have been studied [158, 159].

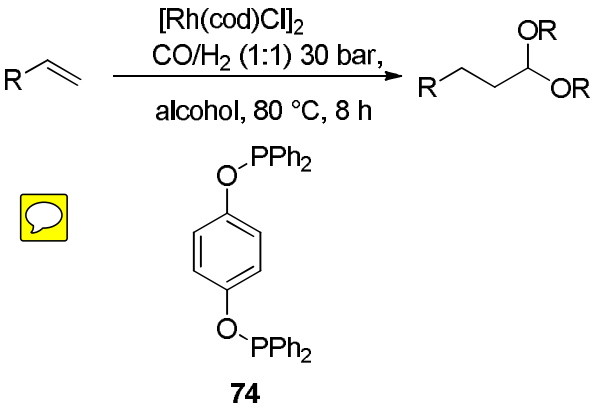
The Rhodium-catalyzed tandem hydroformylation–acetalization of the terpenes 3-carene, 2-carene, α-pinene, and β-pinene was studied in ethanol [160]. In the Rh/P(O-*o*-*t*BuPh)$_3$ system, various fragrance acetals and aldehydes were obtained from these substrates in nearly quantitative combined yields. The process was performed under mild conditions, in ethanol as a solvent, and in the absence of acid cocatalysts (Scheme 53).

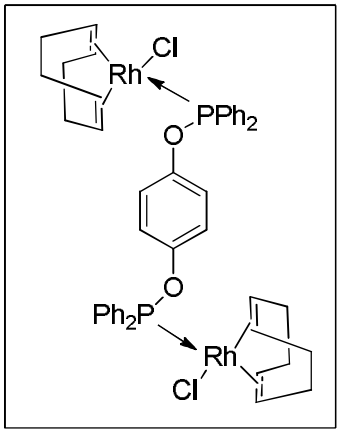
Scheme 53. Hydroformylation/acetalization of α-pinene, and β-pinene



A simple and efficient Rh-phosphinite catalyst **74** was studied for the selective hydroformylation of various olefins [161]. High activity and selectivity for acetal formation was achieved in the absence of co-catalysts with TONs of 2500. The developed protocol works for a wide range of olefins to synthesize corresponding aldehydes and acetals (Table 18).

Table 18. Hydroformylation/acetalization of olefins



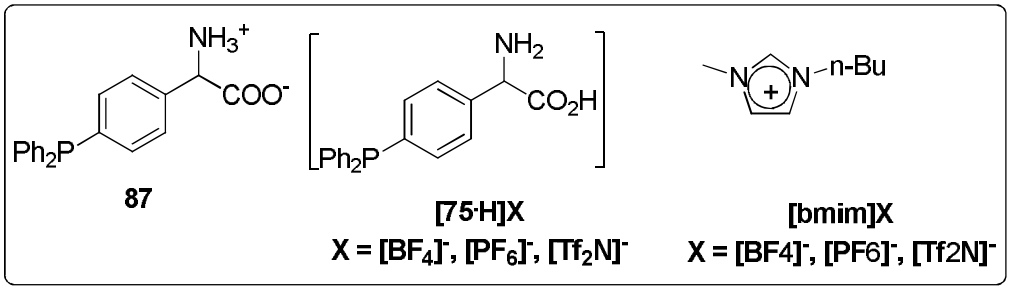


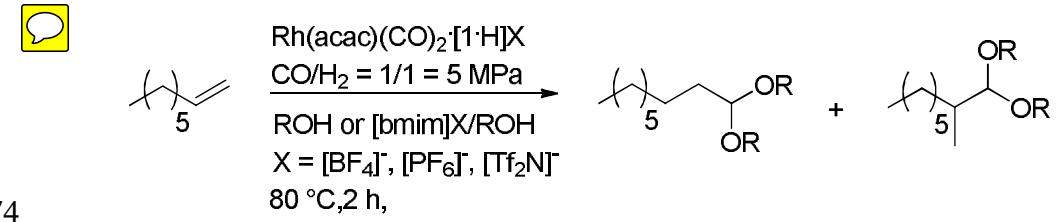
Entry	olefin	alcohol	Acetal (%)	l/b %
1		CH_3OH	99	46:54
2		EtOH	98	55:45
3		nBuOH	81	62:38
4		CH_3OH	99	38:62
5		CH_3OH	98	37:63
6		CH_3OH	97	39:61
7		CH_3OH	99	36:64
8		CH_3OH	98	/
9		CH_3OH	99	/

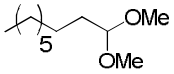
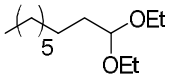
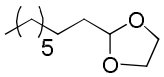
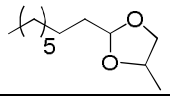
Recently, biphasic hydroformylation using ionic liquids (ILs) as reusable supports of Rh-catalyst has received attention [162].The key issue in IL biphasic hydroformylation is effective immobilization of Rh-catalyst in ILs to avoid Rh loss.

To achieve long-term recycling of Rh-catalyst, system consisting of Brønsted acid–Rh bifunctional catalysts, imidazole- based ionic liquids and alcohols, using a glycine tagged zwitterionic phosphine ligand **75** and its ammonium salts was developed (Table 19) [163].

Table 19. One-pot hydroformylation–acetalization using Rh-[**75**·H][BF4] in [bmim][BF4]–alcohols systems





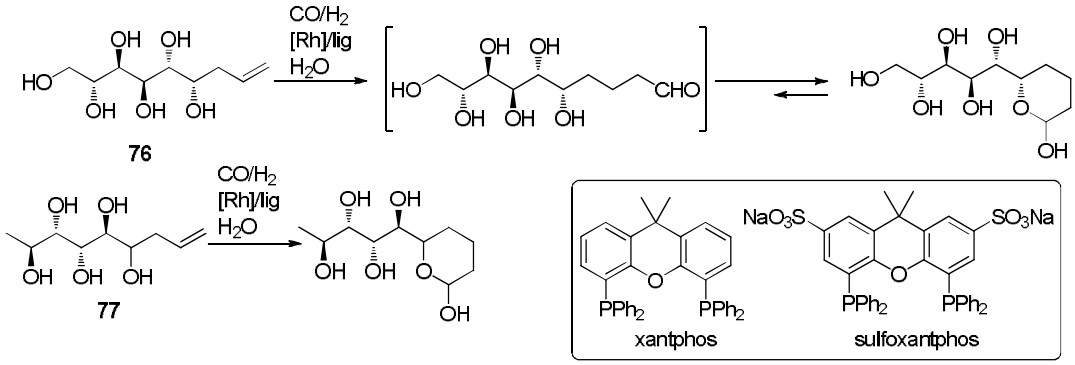
Entry	Main product	Soxo (%)[a]	l : b
1		97	75 : 25
2		84	74 : 26
3		94	76 : 24
4		97	77 : 23

[a] Soxo (selectivity for total oxo products including aldehyde and acetal) characterizes the hydroformylation efficiency of the Rh active site.

6.2 Intramolecular acetalization reaction

Rh-catalysed hydroformylation of polyhydroxylated alkenes i.e. aldehydes bearing an additional hydroxyl group undergo an intramolecular acetal formation giving functionalized lactols as products. Compounds **76** and **77** were used as substrates for hydroformylation leading to spontaneous formation of lactols by subsequent intramolecular cyclisation [164]. For this purpose, the commercially available bidentate xantphos ligand was applied as well as the water-soluble counterpart, sulphoxantphos (Scheme 54).

Scheme 54. Synthesis of lactols via hydroformylation/intramolecular acetalization



Conclusions

Vast number of new reaction sequences under hydroformylation conditions has been developed in the past decade. Arguably, one of the most important advances in the field is the application of chiral enantiomericaly pure organocatalyst catalyzed processes coupled with formation of aldehydes through hydroformylation reaction.

These reaction sequences give expeditive route towards enantioenriched fine chemicals starting from widely available and cheap olefins. Hydroformylation reaction is generally considered a bulk chemistry cornerstone reaction, however, nowadays we are witnessing its progress towards more complex molecules. Further advances in the area, consisting of several different approaches towards indole synthesis and towards other nitrogen containing heterocycles, alkaloids, and other biologically active compounds are already turning hydroformylation into one of the methods to be considered even in the comlpex syntheses of natural products and other fine chemicals.

The past decade has seen an explosion in the development and application of tandem catalysis in general. Further advances will be driven by the continuously expanding importance of transition metal catalysis in organic synthesis, and the potential of tandem catalysis to achieve higher molecular complexity while limiting catalyst and process costs. The parallel investment of effort in organic reaction design, and in deconvoluting the inorganic/organometallic chemistry underlying catalyst transformation, will offer key opportunities for the development of sophisticated synthetic strategies incorporating new tandem catalyses.

Acknowledgements

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