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Synthetic Aspects of Stereoselective Hydroformylation

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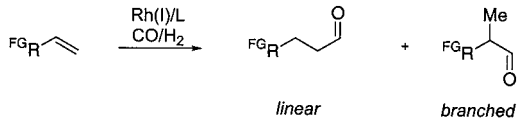
ABSTRACT
The hydroformylation of olefins is well known as one of the industrially most important processes which rely on homogeneous catalysis. Additionally, the hydroformylation represents an ideal atom economic C/C-bond forming reaction with unique opportunities for application in target-oriented organic synthesis, provided that selectivity and in particular stereoselectivity in the course of this metal-catalyzed addition reaction can be controlled. This Account describes recent developments on new and efficient concepts making use of substrate-direction to control stereoselectivity throughout the course of the hydroformylation reaction. Emphasis is given to the concept of substrate-bound catalyst-directing groups which allow for high levels of acyclic stereocontrol. Applications of these new stereoselective variants of the hydroformylation reaction in the context of organic synthesis are discussed. Additionally, recent applications of stereoselective hydroformylation as part of Domino-type processes are covered.

Introduction

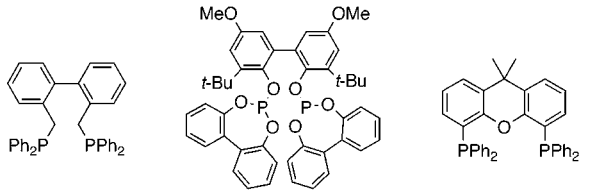
The hydroformylation of olefins, which was discovered as early as 1938 by Otto Roelen, has become one of the largest industrially applied processes which is based on homogeneous catalysis.[1] More than 7 million tons of oxo products are produced per year, of which the majority stems from propene hydroformylation, with butanal and butanol being the major products.[2] These commodities end up mainly as butyl acrylate, which is an important comonomer for the production of polymer dispersion.

In addition to this industrial aspect, the hydroformylation of olefins is an attractive synthetic transformation. Thus, addition of CO and H_2 to an alkene function provides a new carbon−carbon and a new carbon hydrogen bond. Both bond forming events could eventually lead to the formation of a new stereocenter. Simultaneously, the reaction introduces the synthetically useful aldehyde function, which prepares the product for additional carbon skeleton expanding operations. The reaction needs only catalytic amounts of a late transition metal catalyst, with rhodium(I)complexes being the most active and selective catalysts for this reaction, and all atoms of the starting materials remain incorporated into the product. Hence, this reaction is a prototype of an atom economic transformation as defined by Trost with all its associated economic and environmental advantages.[3] From a synthetic aspect, it is interesting to note that a benefit of the alkene function is its inertness to a large set of reagents and conditions, which allows this functionality to be carried through a number of steps in a synthetic sequence, until the final one carbon chain elongation via hydroformylation is desired.

Scheme 1. Hydroformylation of Alkenes



Scheme 2. Ligands for Regioselective Hydroformylation of Terminal Alkenes



BISBI (**1**) *linear : branched* 66 : 1 for 1-hexene

BIPHEPHOS (**2**) *linear : branched* > 40 : 1 for a wide range of functionalized alkenes

XANTPHOS (**3**) *linear : branched* 53 : 1 for 1-octene

However, despite these advantages and contrary to its industrial importance, the hydroformylation has not been of frequent use in organic synthesis yet. This discrepancy is primarily due to the difficulty to control selectivity throughout the course of the hydroformylation reaction.[4]

Thus, historically the most important breakthrough occurred in 1968 with Wilkinson's discovery of phosphine modified rhodium complexes as highly active and chemoselective hydroformylation catalysts.[5] These catalysts eliminated the problem of alkene isomerization and hydrogenation, which were typical side reactions of the original cobalt catalysts. Furthermore a plethora of functional groups was tolerated by these type of catalysts.[4] This initiated extensive studies on the effect of ligands on hydroformylation performance of the corresponding rhodium catalysts. In 1987 the first highly *n*-selective rhodium catalysts were reported.[6] Soon after that, the underlying principles which govern regioselectivity were unraveled.[7,8,9] Today the best catalysts to achieve high levels of *n*-selectivity are those rhodium catalysts derived from the bidentate ligands BISBI,[8] BIPHEPHOS,[9] and XANTPHOS.[10]

Many chiral diphosphine ligands have been evaluated with regard to induce enantioselectivity in the course of the hydroformylation reaction.[11] However, a real breakthrough occurred not earlier than 1993 with the discovery of the BINAPHOS ligand by Takaya and Nozaki.[12]

This discovery provided the first efficient and rather general catalyst for enantioselective hydroformylation of

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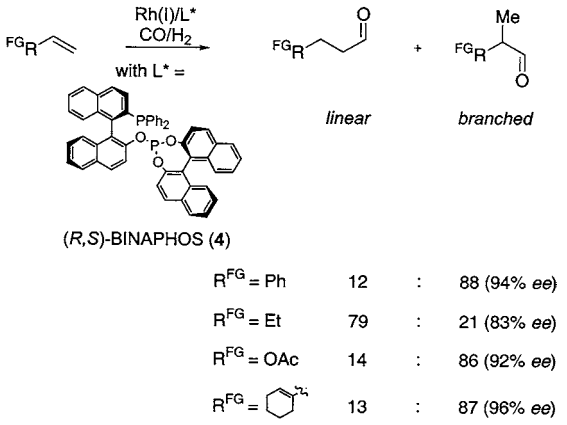
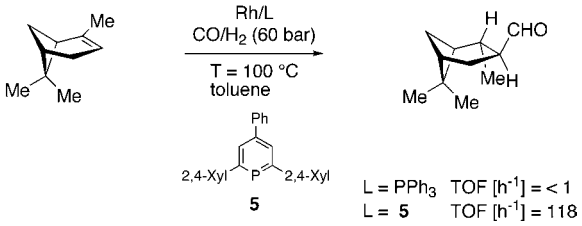
Scheme 3. Enantioselective Hydroformylation of Alkenes



Scheme 4



several classes of alkenes such as arylalkenes, 1-heteroatom functionalized alkenes, and substituted 1,3-dienes and is still the benchmark in this area. But still the most difficult problem with these enantioselective hydroformylations is the simultaneous control of both, enantio- and regioselectivity which limits the structural variety of suitable alkenes for enantioselective hydroformylation significantly (Scheme 3).[4]

An alternative approach to a stereoselective hydroformylation might arise via substrate control of a chiral alkenic starting material. This area was largely unexplored in terms of organic synthesis although it might give rise to the efficient construction of synthetically useful building blocks (vide infra). A number of solutions to the problem of substrate-based stereocontrol in the course of the hydroformylation have been developed and will be surveyed in this review. Particular emphasis will be given to substrate-directed hydroformylations employing catalyst-directing groups. Development of this methodology as well as applications in organic synthesis are the major focus of this account. Additionally, recent applications of stereoselective hydroformylation as part of Domino-type processes are covered.

Diastereoselective Hydroformylation—Cyclic Systems. Substrate-based stereocontrol of alkenic substrates in the course of the hydroformylation was known to be restricted to conformationally defined bicyclic architectures which allow for an efficient energetic discrimination of the competing catalyst trajectories. The diastereoselective hydroformylation of α-pinene provides an instructive example (Scheme 4).[13]

Since tri- and tetrasubstituted alkenes show only modest reactivity against standard hydroformylation catalysts, this reaction could be realized in the past with unmodified

Scheme 5

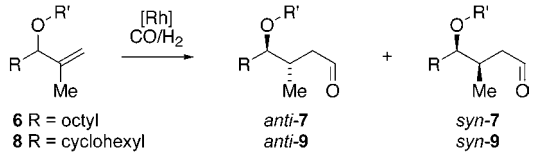


Table 1. Hydroformylation of Methallylic Alcohol Derivatives 6 and 8[a]

entry	substrate	R′	conversion	anti:syn
1	**6**	H	99	53:47
2	**6**	Bz	99	54:46
3	**6**	Piv	90	61:39
4	**6**	TBDPS	99	61:39
5	**8**	H	96	52:48
6	**8**	Ac	84	78:22
7	**8**	Piv	89	82:18
8	**8**	TBS	91	75:25
9	**8**	TBDPS	96	69:31

[a] 1 mol % [$Rh(CO)_2acac$)], 81 bar CO/H_2 (1:1), 80 °C, 48 h.

cobalt catalysts at high pressures and temperatures only. A significant advance with respect to practicality came with the development of new highly active and robust rhodium catalysts which are based on sterically demanding monophosphabenzene ligands such as ligand **5**. These catalysts allowed to run this and other difficult hydroformylation reactions of higher substituted alkenes under significantly milder reaction conditions.[14]

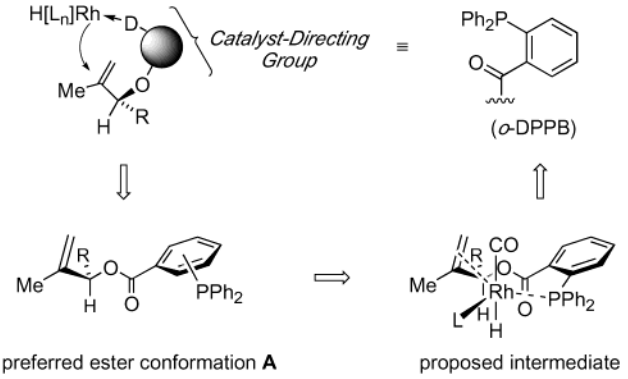
Stereoselective hydroformylation of monocyclic alkenes is much harder to achieve. Good selectivity has been observed in rare cases only, when substrate direction was involved.[15,16]

Acyclic Stereocontrol—Development of a Catalyst-Directing Group. The question of acyclic stereocontrol was until recently an unsolved problem. For example, hydroformylation of acyclic methallylic alcohol derivatives **6** and **8** probing 1,2-asymmetric induction serves well to illustrate the difficulties.[17] These substrates have an intrinsic preference to provide the linear hydroformylation product furnishing γ-hydroxyalkanals **7** and **9** (or their cyclic isomers, γ-lactols for R′ = H), which reduces the selectivity problem to that of diastereoselectivity. From a synthetic point of view this reaction provides an appealing access to homoaldol adducts, thereby creating a new stereocenter in β-position. It was hoped that, similar to the well-established hydroxyl-directed rhodium-catalyzed hydrogenation of allylic alcohols, substrate direction could provide useful levels of diastereoselectivity.[18]

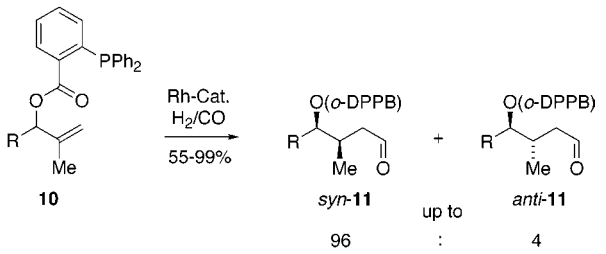
However, best results in the course of the hydroformylation were obtained with the pivalate of **8** with a anti:syn ratio of 82:18 (Table 1, entry 7). Obviously, the hydroxy group was not able to play a similar role in the course of the hydroformylation as it does in the corresponding hydrogenation reaction, namely, to perform as an efficient directing group.

One solution to this problem might be to modify the hydroxy group in such a way as to become an efficient catalyst-directing group (Scheme 6).[19,20] Toward this goal such a group would have to meet several requirements. First it should be a competetive ligand for the rhodium(I)

Scheme 6. Concept of a Substrate-Bound Catalyst-Directing Group



Scheme 7



catalyst in the presence of a large excess of carbon monoxide, which is known to be an excellent ligand for a rhodium(I) center and which is presumably the reason the hydroxyl group failed to act as an efficient director. Thus, a rather efficient ligand as the binding element for the catalyst-directing group was required. Simultaneously, it was mandatory to provide reversible binding to allow for turnover, and hence, catalysis. A monodentate triarylphosphine would be a good candidate. Its reversible binding to rhodium under hydroformylation conditions was known. The most important question had to address the nature and geometry of the linkage between the hydroxy function and the phosphine binding poste. Of course, geometry should be such as to force the substrate to pass a cyclic transition state, which should be highly ordered to allow for an efficient energetic differentiation of the competing diastereomorphic transition states. Thus, an ester linkage between triarylphosphine and hydroxy group was envisioned to be ideal, since it is not only easily formed and cleaved, but additionally, induces the preferred conformation **A** typical for an ester of a secondary alcohol, due to minimization of allylic 1,3 strain. Positioning of the diphenylphosphanyl binding unit ortho relative to the ester linkage should allow the desired two point binding mode of the substrate. Fortunately, the required *ortho*-diphenylphosphanyl benzoic acid is readily obtained in multigram scale and is even commercially available.[21]

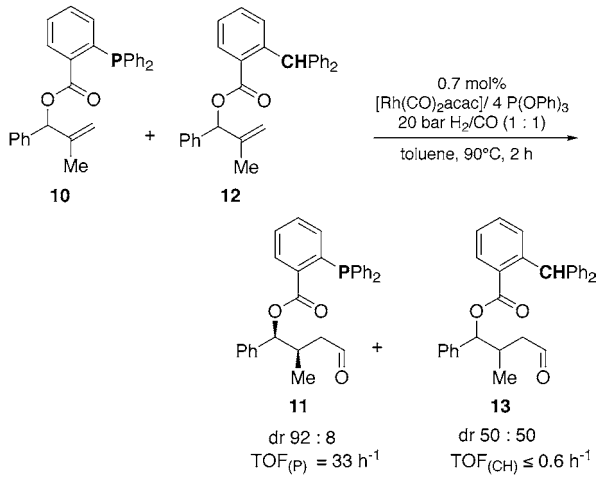
The *ortho*-diphenylphosphanylbenzoates **10** were easily prepared employing standard esterification techniques in excellent to quantitative yields.[20] The hydroformylation of methallylic *o*-DPPB esters **10** provided the corresponding *syn*-aldehydes **11** with diastereoselectivities up to 96:4 and in good to excellent yields (Scheme 7, Table 2).[19,20]

Table 2. Results of Diastereoselective Hydroformylation of Acyclic Methallylic Alcohol *o*-DPPB Esters 10[a]

R	yield [%]	dr (syn:anti)
Ph	99	92:8
i-Pr	98	96:4
Cy	81	95:5
CO_2Me	80	90:10
Et	81	73:27
Bn	75	80:20
	90	96:4
	55	92:8

[a] Reaction conditions and reagents: 0.7 mol % $[Rh(CO)_2acac]$, 2.8 mol % $P(OPh)_3$, 20 bar CO/H_2 (1:1), toluene, 90 °C, 24 h.

Scheme 8. Probing the Role of the *o*-DPPB Group



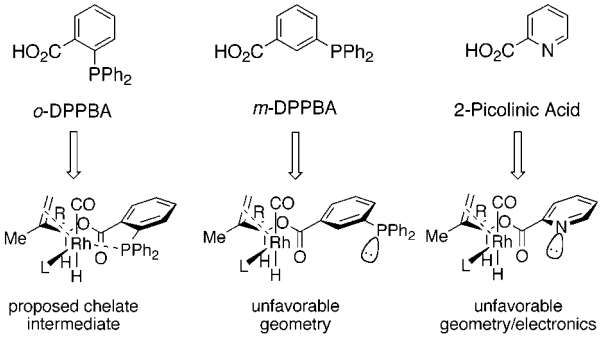
Removal and recycling of the *o*-DPPB group is possible upon alkaline hydrolysis of aldehydes **11** to give in quantitative yields both the γ-lactols as well as the *ortho*-diphenylphosphino benzoic acid.[20]

Support for the role of the *o*-DPPB substituent to act as a catalyst-directing function provided the competition experiment of *o*-DPPB substrate **10** (R═Ph) with the phosphine free benzoate **12**. Thus, exchanging the phosphorus atom of the *o*-DPPB group via a methine unit, itself unable to coordinate to the catalytically active rhodium center, caused a complete loss of stereoselectivity. Furthermore, a significant rate accelerating effect caused by the *o*-DPPB group is indicative of an intramolecular reaction pathway.[20,22]

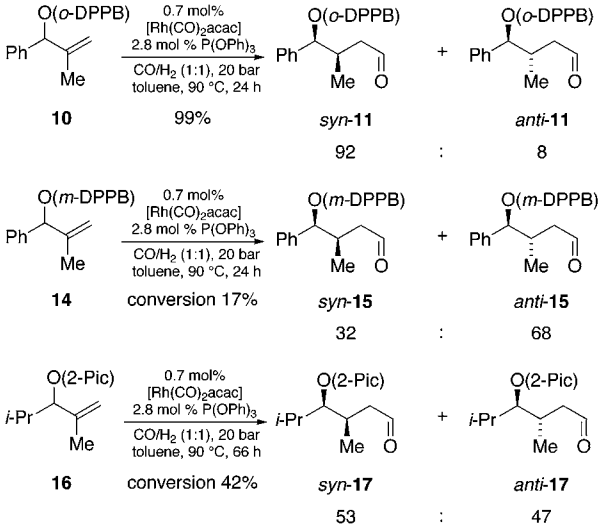
To probe the size and geometry of the chelate ring of the methallylic *o*-DPPB substrates, the *meta*-DPPB substrate **14** and the picolinic ester **16** were studied. The *meta*-DPPB substrate **14** should have a geometry unsuited for chelate formation. The same holds for the picolate **16**. Accordingly, in both cases the hydroformylation not only proceeded stereounselectively, but showed a significantly reduced reaction rate compared to the *o*-DPPB derivative **10**.[22]

To get insight into the role of the ester linkage of the *o*-DPPB group, substrate **18** employing a benzyl ether linkage toward the triarylphosphine binding poste was prepared and its hydroformylation reaction studied.[23]

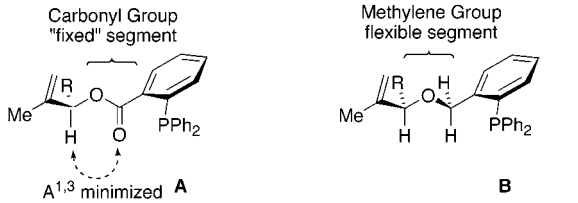
Scheme 9. Probing Geometrical Requirements for an Efficient Catalyst-Directing Group



Scheme 10



Scheme 11. Role of the Ester Linkage of the *o*-DPPB Group

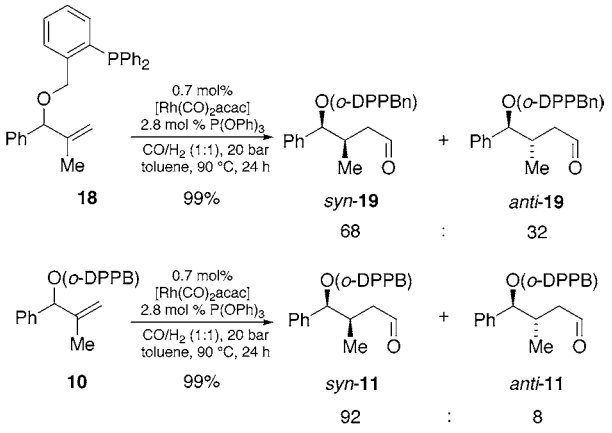


Thus, exchanging the ester segment via the flexible benzyl ether linkage resulted in a significant loss of diastereoselectivity, which confirms the important role of the ester linkage.

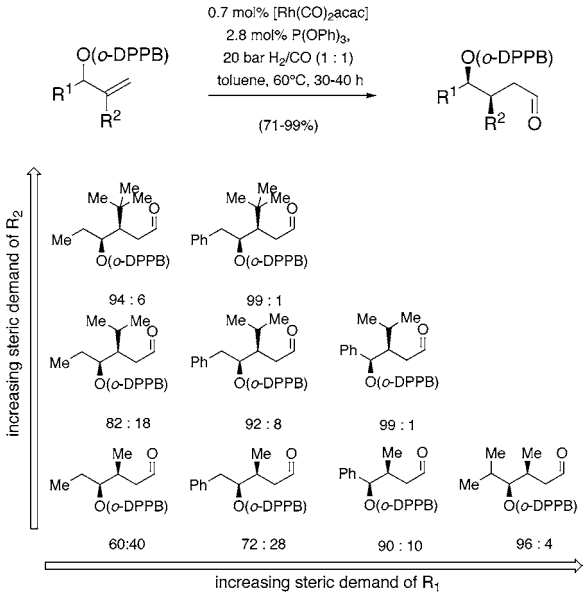
Model for the Origin of 1,2-Asymmetric Induction. In further studies it was observed that diastereoselectivity is a function of the steric demand of both the substituent at the controlling stereocenter R^1 and the substituent at the 2-position of the allylic alcohol system R^2. Increasing the size of both increases diastereoselectivity (Scheme 13).[23]

Thus, considering the hydrometalation step as the selectivity determining step in the hydroformylation reaction, a simple model can rationalize the experimentally observed diastereoselectivities. Since the hydrometalation step is known to be exothermic, the starting diastereomeric alkene complexes **I** and **II** should serve as good models for the corresponding competing diastereomorphic hydrometalation transition states. Hence, a repulsive

Scheme 12. Probing the Role of the Ester Linkage of the *o*-DPPB Group



Scheme 13. Diastereoselectivity of the Hydroformylation of 2-Substituted Allylic *o*-DPPB Esters as a Function of Steric Demand of Substituents R^1 and R^2

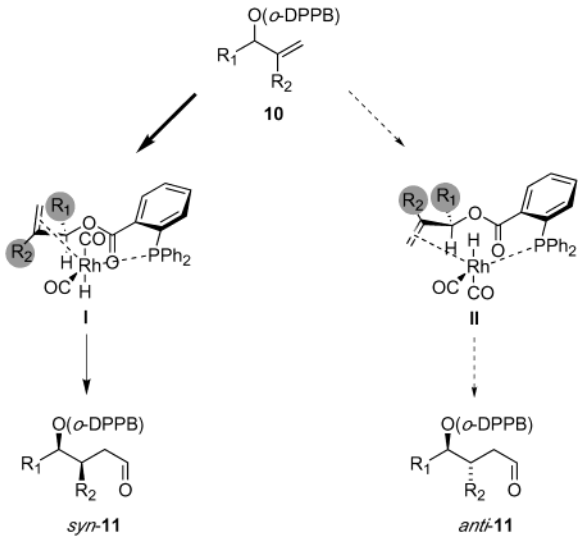


interaction between substituents R^1 and R^2 within complex **II** and the corresponding transition state favors the pathway via intermediate complex **I** leading to the syn diastereomer as the major product.[23]

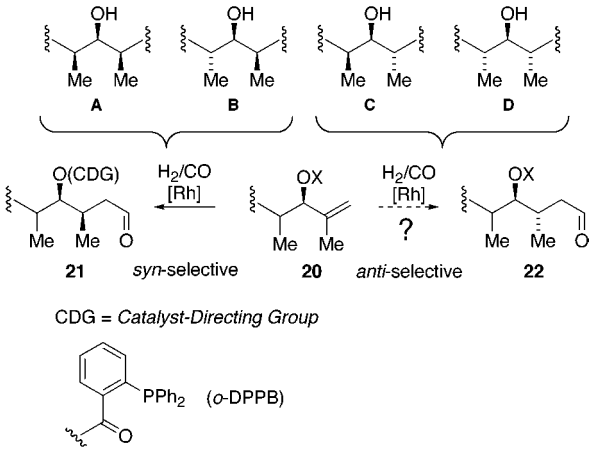
Hydroformylation as the Key Step for the Construction of Stereotriad Building Blocks for Polypropionate Synthesis. With this methodology in hand, we wondered whether the hydroformylation could serve as a key step toward construction of building blocks for polypropionate synthesis.[24] A particular useful strategy is to divide longer polypropionate chains into shorter subunits consisting of an alternating methyl-hydroxyl-methyl array. The term stereotriad has been coined for building blocks of this type.[25] Subsequent combination of these units with the aid of fragment coupling reactions allows the construction of more elaborate polyketide chains. Four different stereotriads may be differentiated (**A**–**D**, Scheme 15).

Thus, starting from a methallylic alcohol system of type **20**, a syn-selective hydroformylation should give access to stereotriad building blocks **A** and **B**.

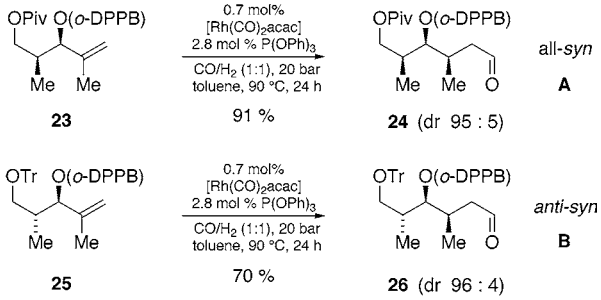
Scheme 14. Proposed Model for the Origin of 1,2-Asymmetric Induction



Scheme 15. Construction of Stereotriad Building Blocks for Polyketide Synthesis through Stereoselective Hydroformylation



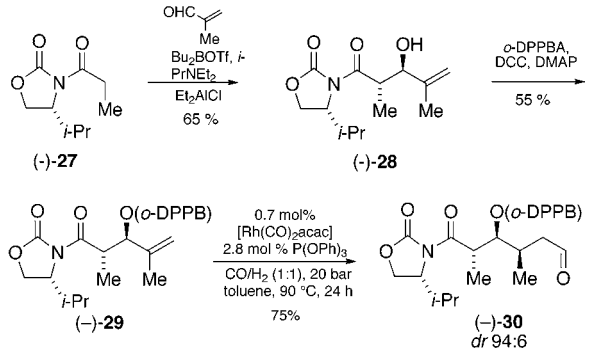
Scheme 16



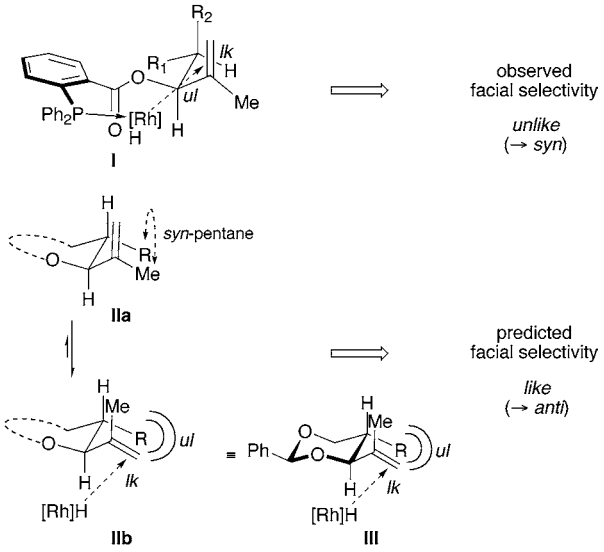
In fact hydroformylation of the corresponding methallylic *o*-DPPB esters **23** and **25** gave in good yield on a multigram scale and with excellent diastereoselectivity the corresponding stereotriad building blocks **24** and **26**.[24] These building blocks are ideally equipped with functional groups to allow a facile chain extension into both directions of the main chain.

Access to an enantiomerically pure anti−syn stereotriad building block (−)-**30** provided for instance a combination of the Evans aldol addition with the *o*-DPPB-directed hydroformylation (Scheme 17).[24]

Scheme 17



Scheme 18. Model for the Development of an anti-Selective Hydroformylation

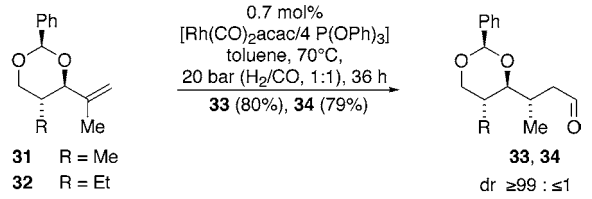


However, to get access to stereotriads **C** and **D** an anti-selective hydroformylation reaction became mandatory.[26] According to the model depicted in Scheme 18, the catalyst-directing *o*-DPPB group delivers the rhodium catalyst to the *ul* face of the alkene (**I**) preferentially, which results into a syn-selective hydroformylation. To achieve an anti-selective hydroformylation, the catalyst had to be forced to approach the *lk* face of the alkene function. This task was solved by incorporating the allylic alcohol system into the cyclic benzylidene acetal **III**. Avoidance of a repulsive *syn*-pentane interaction between R and the methyl group at the alkene as (**IIa**) would give rise to a preferred orientation of the alkene as indicated in **IIb** and **III**. Additionally, the R substituent would shield the *ul* face of the alkene, which forces the catalyst as to approach from the *lk* face.

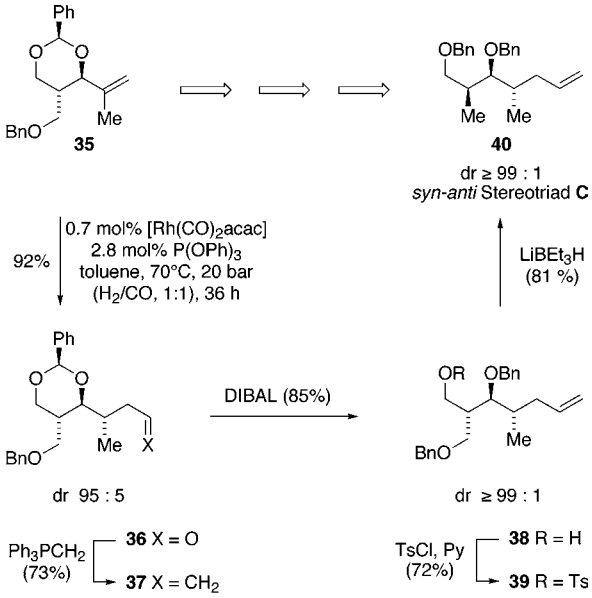
In accord with this model, a highly anti-selective hydroformylation of benzylidene acetal derivatives **31**, **32** to give the all anti-stereotriad building blocks **33**, **34** in good yield and excellent stereoselectivity.[26,27]

However, starting from the corresponding *syn*-benzylidene acetal diastereoselectivity upon hydroformylation was low. Although expected, because of the controlling methyl group occupying here an axial position, access to the missing syn−anti stereotriad **C** was not possible along this line. However, an alternative approach to this missing

Scheme 19. Construction of Stereotriad D



Scheme 20. Construction of Stereotriad C



stereotriad **C** was found starting from the benzyloxy-substituted benzylidene acetal **35**.[26] anti-Selective hydroformylation gave the aldehyde **36**. Protection of the aldehyde, i.e., as an alkene by way of the Wittig olefination protocol, followed by standard functional group manipulations gave stereotriad **C** building block **40** in good overall yield and selectivity. Thus, all four stereotriads **A**−**D** can be reached employing hydroformylation methodology, which paves the way for applications in polyketide synthesis.

For instance the macrolide bafilomycin constitutes an attractive target due to its interesting biological profile. Following the convergent retrosynthetic analysis, described by Toshima et al., the synthesis of the key building block **41** was envisioned. The synthesis was achieved starting from aldehyde **33**. Corey-Fuchs chain elongation followed by protecting group manipulations gave the desired building block in a short and efficient synthetic sequence.[26]

The same principle of acyclic stereocontrol based on minimization of *syn*-pentane interaction is operative in the stereoselective hydroformylation of C-glucoside derivatives **45**. Thus, diastereoselectivity increased with the size of the substituent R (Table 3), which underlines the important role of the 2-OR substituent with respect to stereoselectivity control.[28]

A new catalyst-directing group based on a methylen phosphafluorenyl function was introduced recently by Leighton et al. This group enabled the simultaneous control of regio- and diastereoselectivity to furnish the

Scheme 21. Retrosynthesis of Bafilomycin A_1 and Synthesis of a Key Building Block

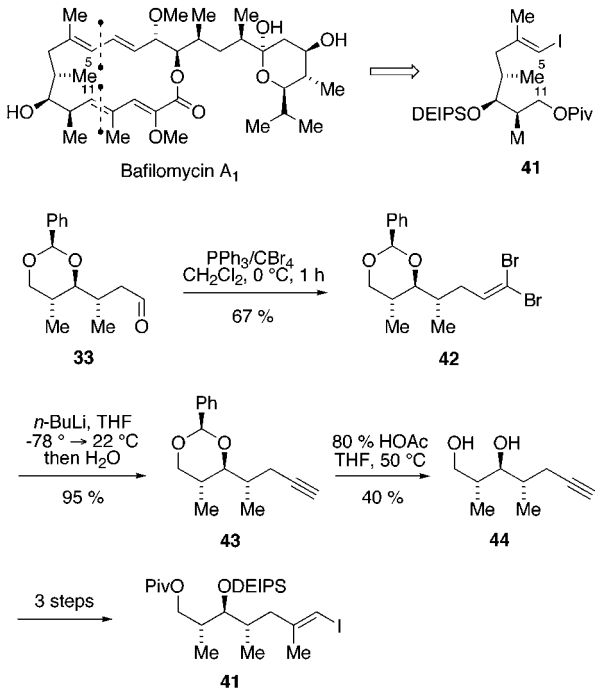
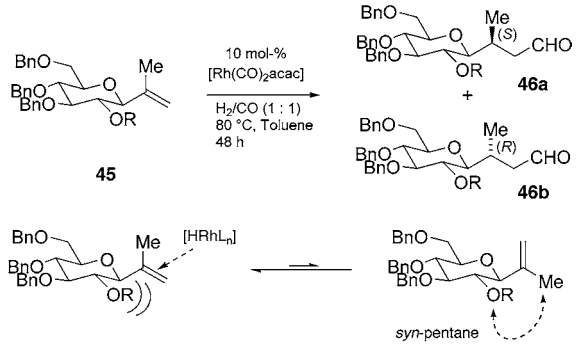


Table 3. Hydroformylation of 1,1-Disubstituted C-Glycosylated Alkene Derivatives 45

R	yield	**46a**:**46b**
H	81	83:17
Piv	91	90:10
Bz	99	97:3
Ac	99	98:2
TBS	99	>99:<1

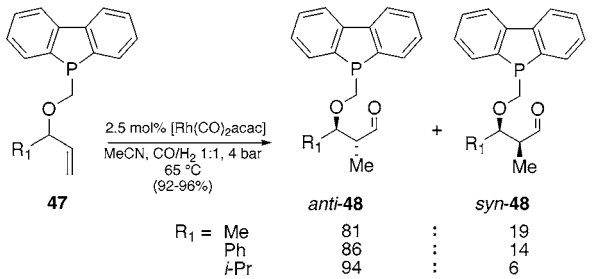
Scheme 22



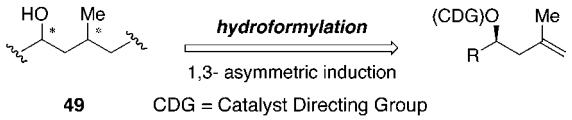
anti-aldol derivatives **48** in good yield and diastereoselectivity.[29]

1,3-Asymmetric Induction. A further quite common structural motif within the polyketide class of natural products possesses hydroxy- and methyl-substituted stereocenters in a 1,3-relation at an acyclic main chain. In this case an ideal starting material would be a homomethallylic alcohol derivative, since a stereoselective hydroformylation would give access to the desired building blocks **49**.[30,31] This requires efficient 1,3-asymmetric induction, which is generally more difficult to achieve than 1,2-asymmetric induction, because of additional degrees of freedom.

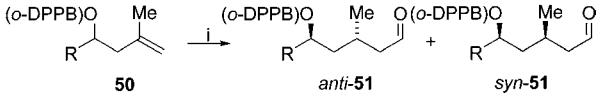
Scheme 23



Scheme 24. Proposed Construction of Polyketide Building Block 49



Scheme 25. Stereoselective Hydroformylation of Homomethallylic *o*-DPPB Esters 50[a]

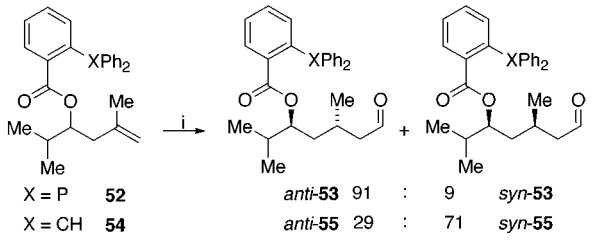


[a] Reagents and conditions: (i) 0.7 mol % $[Rh(CO)_2acac]$/2.8 mol % $P(OPh)_3$, 20 bar CO/H_2 (1:1), toluene.

Table 4. Results of the Diastereoselective Hydroformylation of Homomethallylic *o*-DPPB Esters 50

R	*T* [°C]	*t* [h]	yield [%]	anti:syn
i-Pr	50	72	93	91:9
i-Pr	70	24	99	87:13
i-Pr	90	24	99	70:30
Cy	50	72	90	91:9
Hex	30	168	81	90:10
Ph	30	120	72	90:10
o-$MeOC_6H_4$	30	240	78	90:10
(*E*)-EtCH=CMe	30	168	85	90:10

Scheme 26. Probing the Role of the *o*-DPPB Group



Interestingly, employing the catalyst-directing *o*-DPPB group allowed a diastereoselective hydroformylation of homomethallylic *o*-DPPB esters to give the *anti*-aldehydes **51** in good yields and diastereoselectivity (Scheme 25, Table 4).[30]

Control experiments with CH-derivative **54** showed that the *o*-DPPB group controls diastereoselectivity and, simultaneously, accelerates the rate of the hydroformylation reaction.[31]

Interestingly, diastereoselectivities are almost independent from the nature of the substituent at the stereogenic center but showed significant temperature dependence.

These two observations, indicated that a preferred reactive substrate conformation inherent to the homomethallylic system itself might be an important element. Hence, the preferred conformation of the homomethallylic *o*-DPPB ester **52** was examined by NMR techniques and the results were confirmed with MACROMODEL/MM3 calculations.[31] Thus, derivative **52** possesses the preferred conformation **A**.

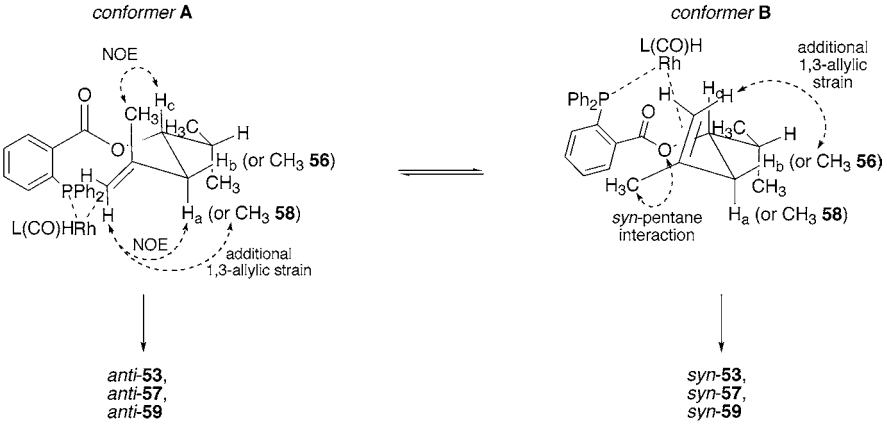
Delivery of the rhodium catalyst as indicated via the catalyst-directing *o*-DPPB group provides the observed anti-major diastereomer anti-**53**. Conformation **B** suffers from an additional *syn*-pentane interaction and should provide the syn-minor diastereomer *syn*-**53**. Support for this model came from two additional experiments. Thus, exchanging H_b with a methyl substituent would disfavor conformation **B** since additional allylic 1,3 strain would arise (Scheme 27). Interestingly, hydroformylation of this anti-derivative **56** provided a significantly higher diastereoselectivity of 96:4 in favor of the predicted isomer anti-**57** (Scheme 28). However, when H_a is exchanged with a methyl substituent, both conformations **A** and **B** suffer from repulsive interactions. Thus, neither formation of the anti nor the syn diastereomer should be favored (Scheme 27). This prediction is congruent with the hydroformylation experiment of syn-derivative **58**, which occurred in a completely stereorandom fashion (Scheme 28).[31]

Another structural motif common to the polyketide class of natural products of current synthetic interest is the skipped polyol motif present in a number of polyacetate derived natural products. An interesting approach to these systems involves the hydroformylation of methylene 1,3-dioxanes **60**. Employing the rhodium/triphenylphosphine catalyst hydroformylation proceeded with good regioselectivity and high diastereoselectivity to give the protected *syn*-3,5-dihydroxyaldehydes **61**, which are well prepared for further polyketide main chain extensions (Scheme 29, Table 5).[32]

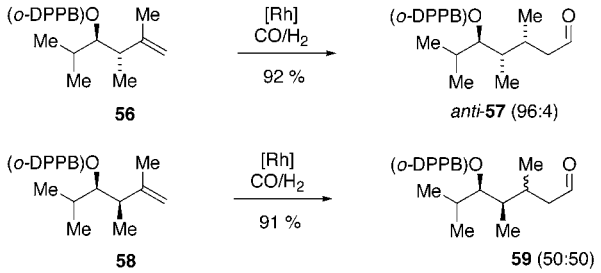
Sequential Transformations Involving Regio- and Stereoselective Hydroformylation as the Key Step. Hydroformylation not only creates a new carbon carbon bond, but it additionally introduces the synthetically useful aldehyde function under rather mild reaction conditions compatible with a wide range of functional groups. That aldehyde function may now serve as a starting point to enable a further expansion of the organic skeleton by a variety of reactions. Ideally, one may couple all of these steps in a one pot operation resulting in so-called sequential or domino-type transformations. Only recently has the synthetic potential of these type of transformations been unraveled.[33]

Hydroaminomethylation. Hydroaminomethylation has been discovered as early as 1943 by Reppe at BASF.[34] Thus, when alkenes were treated with syngas, primary or secondary amines in the presence of an $[Fe(CO)_5]$ catalyst either secondary or tertiary amines **63** or mixtures thereof where obtained (Scheme 30). Hence, the amine products result from consecutive hydroformylation (**62** → **64**), imine or enamine formation and final transition metal catalyzed hydrogenation. However, yields were low and severe conditions were required (up to 390 °C, up to 950 bar). That was in principle a consequence of the low catalyst activity of the $[Fe(CO)_5]$ catalyst employed at that time.

Scheme 27. Model for the Origin of 1,3-Asymmetric Induction



Scheme 28



Scheme 29

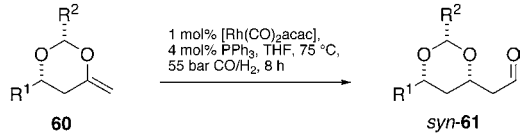
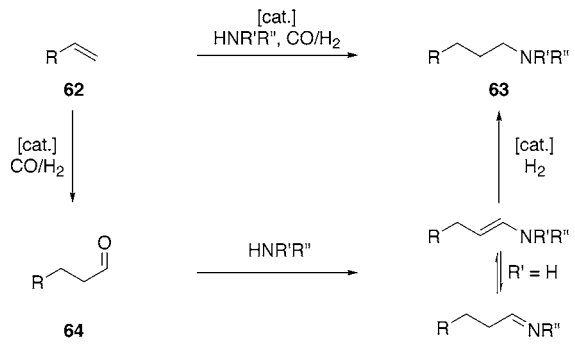


Table 5. Rhodium-Catalyzed Hydroformylation of Substituted 4-Methylene-1,3-dioxanes 60

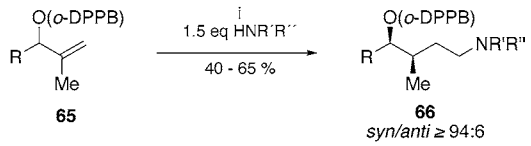
R^1	R^2	yield [%]	*rs*
H	*t*-Bu	81	12:1
Me	*t*-Bu	72	13:1
Me	Me	75	13:1
$BnO(CH_2)_2$	Me	71	9:1

Scheme 30. Mechanism of the Hydroaminomethylation



In the meantime catalysts with a significantly higher activity have been identified. In particular, rhodium catalysts have shown to provide best reactivity and selectivity for a wide range of substrates.[33] However, the slow step is usually the hydrogenation of the enamine/imine (or immonium ion) intermediate.

Scheme 31. Stereoselective Hydroaminomethylation[a]



[a] Reagents and conditions: (i) 0.7 mol % $[Rh(CO)_2acac]$/2.8 mol % $P(OPh)_3$, 20→80 bar CO/H_2 (1:1), 90→120 °C, THF.

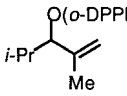
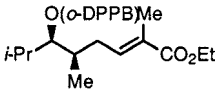
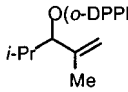
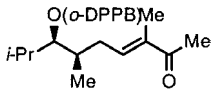
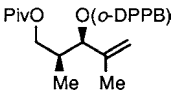
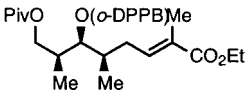
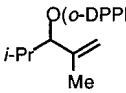
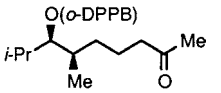
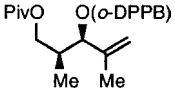
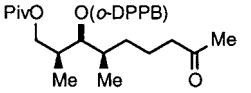
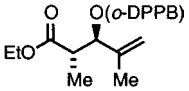
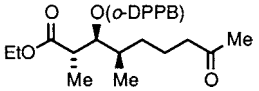
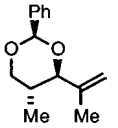
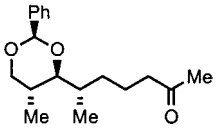
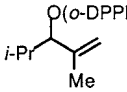
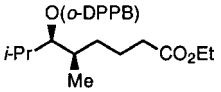
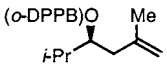
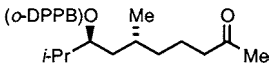
To allow for acyclic stereocontrol in the course of the hydroaminomethylation, one may rely on substrate direction by way of a substrate bound catalyst-directing group. Thus, with *ortho*-diphenylphosphanyl benzoate (*o*-DPPB) as the catalyst-directing group, stereoselective hydroaminomethylation of acyclic methallylic alcohol derivative **65** could be achieved (Scheme 31, Table 6).[35] Both secondary as well as primary amines could be employed to give the corresponding tertiary or secondary amine products **66** in fair to good yields, in diastereomer ratios ≥ 94:6 (syn:anti).

Domino Hydroformylation Mukaiyama Aldol Reaction. β,γ- or γ,δ-unsaturated silyl enol ethers undergo Domino hydroformylation/intramolecular Mukaiyama aldol reaction to form cyclic *O*-silylated aldol adducts in good yields.[36] Thus, γ,δ-unsaturated silyl enol ether **67** provided after *n*-selective hydroformylation and intramolecular aldol addition the bicyclic silyl ether **68** (Scheme 32). Prolonged reaction times promote the formation of the aldol condensation product **69**.

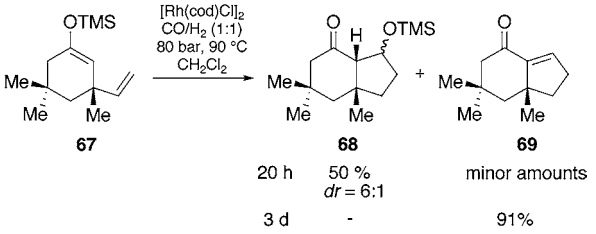
Domino-Hydroformylation-Allylboration-Hydroformylation Sequence. An appealing entry to condensed 1,5-oxazadecaline systems is the domino hydroformylation-allylboration-hydroformylation sequence starting from N-allyl-γ-amidoallylboronate **71**, readily prepared from boronate aldehyde **70** (Scheme 33).[37] Hence, regioselective hydroformylation generates aldehyde **75**, which undergoes a diastereoselective intramolecular allylboration to give vinyl derivative **76**. The reaction does not stop at this stage, since the alkene moiety in **76** undergoes a further *n*-selective hydroformylation to give an equilibrium mixture of lactols **73** and open-chain δ-hydroxy aldehyde **72**.

Reductive removal of the Cbz group from carbamates **72**/**73** furnished in a further domino type process consisting of hydrogenation, cyclization/enamine formation, hydrogenation the indolizidine **74**.

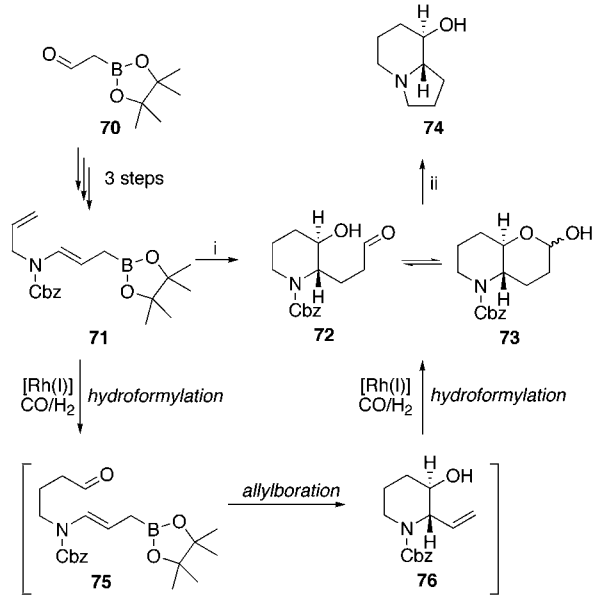
Table 6. Diastereoselective Domino Hydroformylation/Wittig and Domino Hydroformylation/Wittig Hydrogenation Reactions

entry	alkene	ylide	major diastereomer	yield (%)	dr (syn:anti)
1		$Ph_3P{=}CMeCO_2Et$		75	96:4
2		$Ph_3P{=}CMeCOMe$		78	92:8
3		$Ph_3P{=}CMeCO_2Et$		60	92:8
4		$Ph_3P{=}CHCOMe$		70	92:8
5		$Ph_3P{=}CHCOMe$		68	92:8
6		$Ph_3P{=}CHCOMe$		60	90:10
7		$Ph_3P{=}CHCOMe$		78	>98:2
8		$Ph_3P{=}CHCO_2Et$		36	92:8
9		$Ph_3P{=}CHCOMe$		82	91:9

Scheme 32



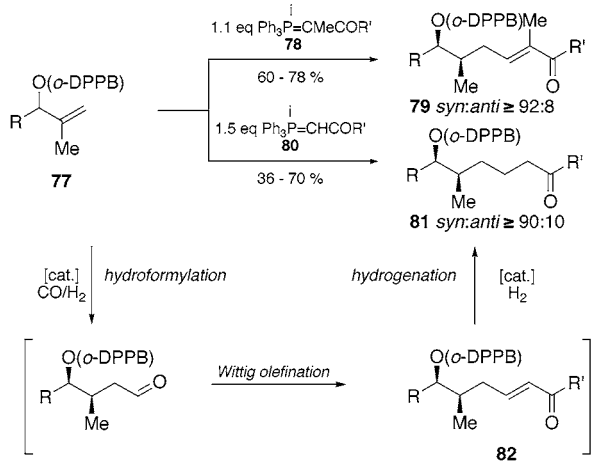
Scheme 33



Domino-Hydroformylation-Wittig olefination-Hydrogenation Sequence. Methallylic and homomethallylic alcohol derivatives reacted under hydroformylation conditions in the presence of stabilized Wittig ylides to the corresponding domino hydroformylation products **79** and **81** in good yields and diastereoselectivities (Scheme 34, Table 6).[38] Stereocontrol was provided either by the catalyst-directing *o*-DPPB group or, alternatively, relying on passive substrate control (entry 7). Disubstituted, stabilized Wittig ylides **78** stopped at the stage of the trisubstituted alkenes **79**. When monosubstituted ylides **80** were employed, the respective α,β-unsaturated carbonyl derivatives **82** experienced further hydrogenation to give saturated derivatives **81**. Hence, the same rhodium catalyst that catalyzed the hydroformylation of alkenes **77** acted upon acceptor substituted alkenes **82** as a hydrogenation catalyst.

Thus, two new carbon−carbon single bonds and a new stereogenic center with high levels of acyclic stereocontrol were formed in one step. Since the hydroformylation is intrinsically tolerant to a large set of functional groups, this domino process may be suited to function as a fragment coupling step in the context of a convergent synthetic strategy.

Scheme 34. Domino Hydroformylation-Wittig Olefination/ Hydrogenation Reaction[a]



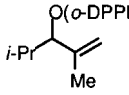
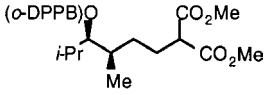
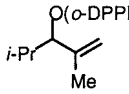
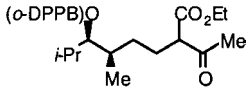
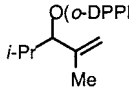
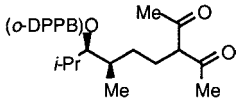
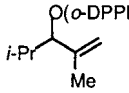
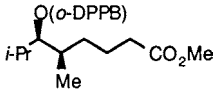
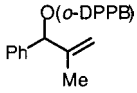
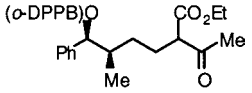
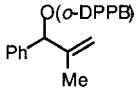
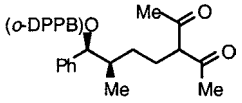
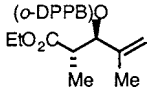
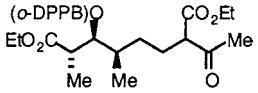
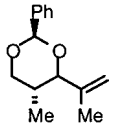
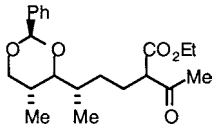
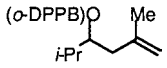
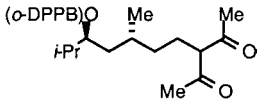
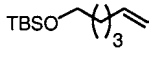
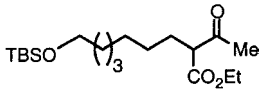
[a] Reagents and conditions: (i) 0.7 mol % $[RhH(CO)(PPh_3)_3]$, 20 bar CO/H_2 (1:1), toluene, 90 °C, 48 h.

Domino-Hydroformylation-Knoevenagel-Hydrogenation Sequence. Although the hydroformylation represents an atom economic reaction, the Wittig olefination as part of the Domino-hydroformylation-Wittig olefination sequence is the reverse. In this context a more appealing olefination reaction is the Knoevenagel condensation with water being the only byproduct.

Thus, subjection of methallylic o-DPPB derivatives **83** to hydroformylation conditions in the presence of stoichiometric amounts of a methylene active derivative and catalytic amounts of piperidinium acetate furnished derivatives **84** in good yield and stereoselectivity.[39] Hence, these products are the result of a sequential hydroformylation, Knoevenagel condensation, and a final rhodium-catalyzed hydrogenation of the electron acceptor substituted alkenic function. Thus, again the same catalyst that catalyzes the hydroformylation step serves as a hydrogenation catalyst during the final step of this Domino process. Malonates, β-ketoesters as well as β-diketones (Table 6) could serve as the methylene active component.

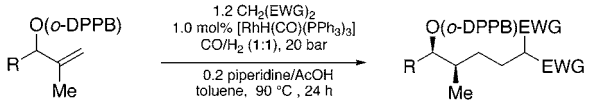
The reaction could be used for the construction of the anti−syn and the all-anti stereotriad sequences (Table 7, entries 7, 8). 1,2-Asymmetric induction was controlled in all those reactions within the hydroformylation step making use of either the substrate-bound catalyst-direct-

Table 7. Results of the Regio- and Stereoselective Domino Hydroformylation/Knoevenagel/Hydrogenation Reaction

entry	alkene	$CH_2(EWG)_2$	product	yield (%)	dr (syn:anti)
1		$CH_2(CO_2Me)_2$		51	96:4
2		$MeCOCH_2CO_2Et$		71	96:4
3		$MeCOCH_2COMe$		52	96:4
4		$HO_2CCH_2CO_2Et$		41	96:4
5		$MeCOCH_2CO_2Et$		64	92:8
6		$MeCOCH_2COMe$		60	92:8
7		$MeCOCH_2CO_2Et$		55	96:4
8		$MeCOCH_2CO_2Et$		62	>98:2
9		$MeCOCH_2COMe$		51	91:9
10		$MeCOCH_2COMe$		64	>99:<1[a]

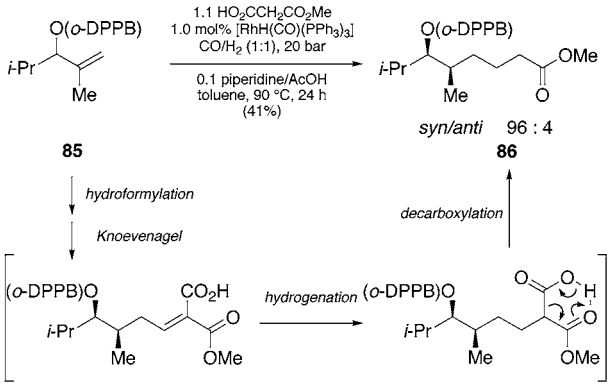
[a] Regioselectivity.

Scheme 35. Domino Hydroformylation/Knoevenagel/Hydrogenation Reaction (EWG = Electron-Withdrawing Group)



83 *syn*-**84**

Scheme 36. Proposed Mechanism of the Domino Hydroformylation-Knoevenagel-Hydrogenation-Decarboxylation Reaction



ing *o*-DPPB group (entries 1−7), or making use of substrate control via conformational constraints (entry 8). The domino reaction could also be applied to a homomethallylic *o*-DPPB ester (Table 7, entry 9). Additionally, a regioselective hydroformylation of a monosubstituted alkene with the BIPHEPHOS/rhodium catalyst could be employed as the key step in this domino process to give the linear β-ketoester in good yield and excellent regioselectivity (see Table 7, entry 10).

When malonic acid monomethyl ester was used, the monoester derivative **86** was formed, which resulted from a Domino process consisting of four steps: *o*-DPPB-directed stereoselective hydroformylation, Knoevenagel condensation, rhodium catalyzed hydrogenation, and a final decarboxylation (Table 7, entry 4, Scheme 36).

Hence, this sequential transformation allows in a single operational step the formation of two carbon−carbon single bonds, with concomitant generation of a new stereogenic center with high levels of regio- and acyclic stereocontrol. Additionally, a synthetically useful β-dicarbonyl function is introduced.[39]

Conclusion and Outlook

Although more than 60 years of active research in the field of hydroformylation in both academia and industry have passed, applications of this industrially important reaction in organic synthesis have been scarce. The main reason for that stemmed from the difficulty to control selectivity throughout the course of the hydroformylation. This situation has significantly improved during the past decade. Thus, control of regioselectivity upon hydroformylation of terminal alkenes in favor of the linear product is possible today. However, there is still no practical solution to achieve a general *iso*-selective hydroformylation of a terminal alkene. Control of enantioselectivity has improved dramatically in the past decade. However, the simultaneous control of regio- and enantioselectivity is still the major problem. Alternatively, during the last years new ways of substrate control of stereoselectivity have been developped on a rational basis, which have opened new avenues for the application of the hydroformylation to target-oriented organic synthesis as outlined in this account. In particular, the employment of substrate-bound catalyst-directing groups was a conceptual advance and a practical solution in this field. But still, a covalent attachment of a directing group requires additional synthetic operations, which may not represent the ultimate solution.

New efforts to devise better solutions to these and other selectivity problems for the hydroformylation reaction seem very much worthwhile. In particular, the chapter on domino reactions should have given a glimpse on what may become possible in terms of organic synthesis if one would have complete control over all aspects of selectivity in the course of this important carbon carbon bond forming reaction.

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