Controlling Stereoselectivity with the Aid of a Reagent-Directing Group: Hydroformylation, Cuprate Addition, and Domino Reaction Sequences

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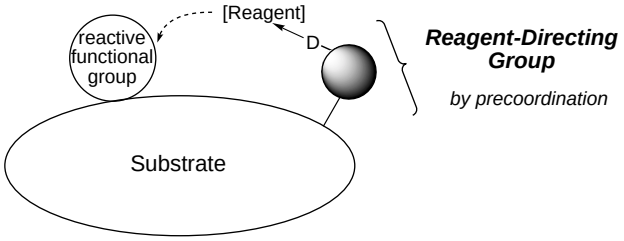
Abstract: The specific introduction of an appropriately designed reagent-directing group into an organic substrate allows the more efficient use of substrate direction to allow high levels of acyclic stereocontrol in both rhodium-catalyzed hydroformylation and cuprate addition to enoates. This provides access to major building blocks of the polyketide class of natural products. Incorporation of these directed reactions into sequential transformations holds promise for new particularly efficient synthetic methods.

Keywords: asymmetric synthesis · catalysis · copper reagents · domino reactions · hydroformylations · rhodium

Introduction

Substrate control can be a useful tool to allow high levels of selectivity in organic reactions. This is particularly valid for reactions in which the reacting substrate is equipped with a functionality suitable to allow precoordination of the reagent followed by intramolecular reagent delivery. This type of reaction, coined by Evans et al. as substrate-directable reactions, is of great synthetic value as proven in numerous total synthesis.[1] However, known substrate-directable reactions rely on the nature of the coordinating functionality present in a particular substrate. This clearly defines limitations to the set of reagents potentially directable by a specific functional group.

A way to overcome such an intrinsic limitation may be to provide a specifically introduced reagent-directing group into an organic substrate (Scheme 1). Such a specifically introduced functionality should have the ability to precoordinate the desired reagent. This would result in an intramolecular pathway for the desired chemical reaction with a corresponding reactive functional group within the substrate. By choosing the appropriate point of attachment of the directing functionality, and by choosing the appropriate geometry of this group, it should be possible to control the trajectory of a particular reagent, which, in turn, should be the ideal basis to control any type of selectivity for a given chemical reaction.



Scheme 1. Concept of a specifically introduced reagent-directing group into an organic substrate as a selectivity control instrument.

Such an approach necessitates two additional synthetic operations: introduction and removal of the reagent-directing group. What at first sight might appear a disadvantage should be acceptable if one could solve the selectivity problem for a synthetically valuable reaction which is otherwise not susceptible to stereocontrol. In this context transition metal catalyzed addition reactions have gained importance because of their intrinsic atom economy and efficiency which may also be beneficial for environmental and economic grounds.[2]

An example is the rhodium-catalyzed hydroformylation reaction, which is an industrially important homogeneous catalytic process.[3] It is amazing that such an important transition metal catalyzed C–C bond-forming process has been employed only rarely in organic synthesis.[4] Part of the reason for this stems from the difficulty in controlling stereoselectivity. Even though some recently developed chiral rhodium catalysts allow enantio- and diastereoselective hydroformylation of certain specific classes of alkenes,[5, 6] little is known about the diastereoselective hydroformylation of acyclic olefins.[7, 8]

Discussion

The difficulty of this task became obvious in an attempt to achieve diastereoselective hydroformylation of a simple

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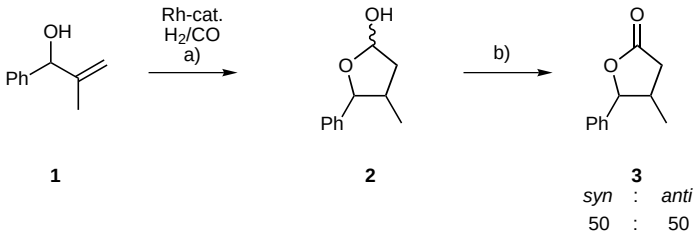
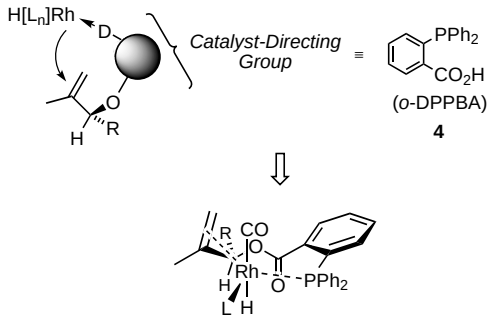
methallylic alcohol system. It was expected that in analogy to the known substrate-directed rhodium-catalyzed hydrogenation reaction, substrate direction through the hydroxy substituent would control diastereoselectivity in the course of the hydroformylation reaction.[9] However, a completely stereorandom formation of the hydroformylation product was observed (**1** → **3**; Scheme 2).[10, 11]



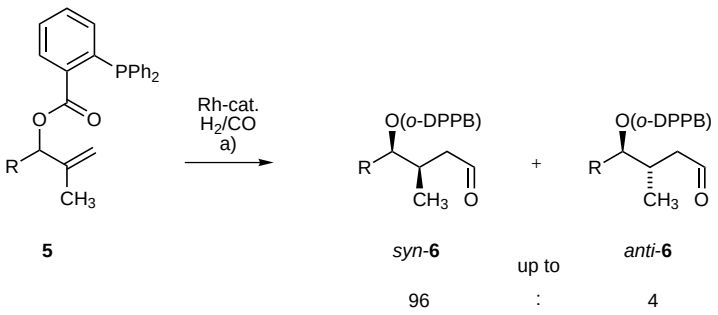
Scheme 2. Reaction conditions: a) 0.35 mol % $[Rh(CO)_2(acac)]$, 7 mol % PPh_3, 20 bar H_2/CO (1:1), toluene, 90 °C, 6 – 24 h (83 – 95 %); b) pyridinium chlorochromate on Al_2O_3, CH_2Cl_2, 25 °C, 16 h (95 %). Hacac = acetyl acetone.

In contrast to rhodium-catalyzed hydrogenation reactions, in the rhodium-catalyzed hydroformylation the hydroxy group does not operate as an efficient catalyst-directing group. This may be primarily due to the carbon monoxide, itself an excellent ligand for rhodium(I), which is present in large excess under hydroformylation conditions. Hence, the hydroformylation reaction is an ideal first case to test the potential of the concept of applying a specifically introduced catalyst-directing functionality to control diastereoselectivity in the course of the hydroformylation reaction. Therefore, a specific catalyst-directing group needed to be designed, which itself had to a) function as a good ligand for rhodium under hydroformylation conditions, b) provide reversible coordination of the catalytically active rhodium species to allow turnover, c) enable facile introduction into the substrate as well as removal from the product, and d) allow a highly ordered cyclic transition state for the stereochemistry-defining step of the hydroformylation reaction.

As an ideal catalyst-directing group for this particular problem the *ortho*-diphenylphosphanylbenzoate system (*o*-DPPB) was introduced (Scheme 3).[10] With the aid of the *o*-DPPB functionality a substrate-directed diastereoselective hydroformylation of methallylic alcohol derivatives was achieved with high levels of acyclic stereocontrol to provide the *syn*-aldehydes **6** as the major diastereomers (Scheme 4).[10]

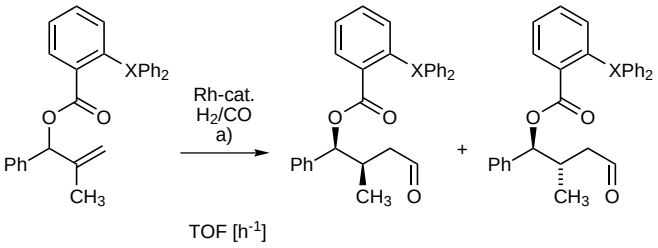


Scheme 3. Design of a catalyst-directing group for the control of diastereoselectivity upon hydroformylation of acyclic methallylic alcohol systems.



Scheme 4. Reaction conditions: a) 0.7 mol % $[Rh(CO)_2(acac)]$, 2.8 mol % $[P(OPh)_3]$, 20 bar H_2/CO (1:1), toluene, 90 °C, 24 h (63 – 99 %).

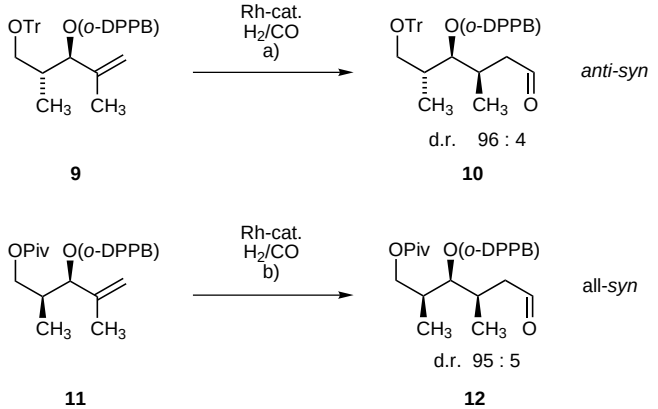
Support for the role of the *o*-DPPB substituent as a catalyst-directing group was provided in a control experiment with the benzoate **7**. Thus, exchanging the phosphorus of the *o*-DPPB group with a CH moiety, itself not able to coordinate to the catalytically active rhodium center, caused a complete loss of stereoselectivity in the hydroformylation reaction (Scheme 5).[10]



		TOF [h^{-1}]				
X = P:	**5a**	21	*syn*-**6a**	92	: 8	*anti*-**6a**
X = CH:	**7**	1.4	*syn*-**8**	50	: 50	*anti*-**8**

Scheme 5. Reaction conditions: a) 0.7 mol % $[Rh(CO)_2(acac)]$, 2.8 mol % $[P(OPh)_3]$, 20 bar H_2/CO (1:1), toluene, 90 °C, 2 h.

The *o*-DPPB-directed hydroformylation of methallylic alcohol derivatives could be applied to the construction of stereotriads—central building blocks of the polyketide class of natural products. Thus, starting from the methallylic *o*-DPPB esters **9** and **11** the *anti-syn* and all-*syn* stereotriad building blocks **10** and **12**, respectively, could be obtained in good yields and diastereoselectivities (Scheme 6).[12]



Scheme 6. Reaction conditions: a) 0.7 mol % $[Rh(CO)_2(acac)]$, 2.8 mol % $[P(OPh)_3]$, 20 bar H_2/CO (1:1), toluene, 90 °C, 24 h (91 %); b) same as a) (70 %).

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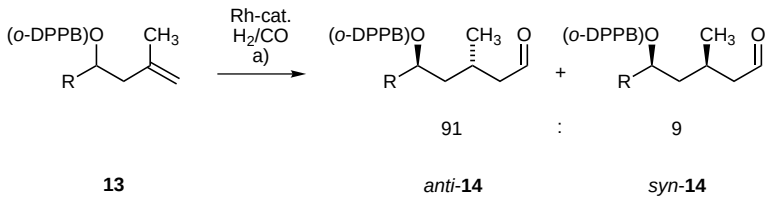
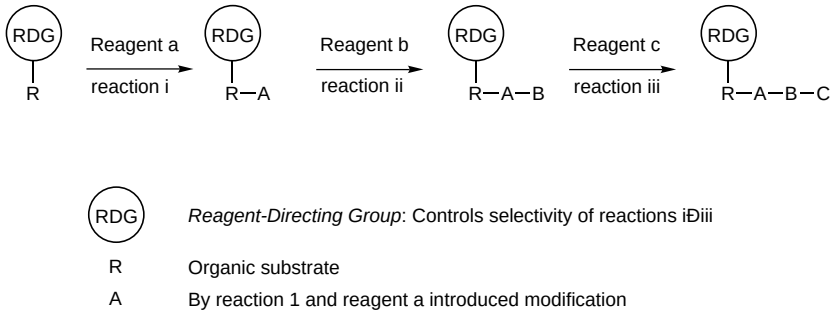


Scheme 7. Reaction conditions: a) 0.7 mol% $[Rh(CO)_2(acac)]$, 2.8 mol% $[P(OPh)_3]$, 20 bar H_2/CO (1:1), toluene, 30–50 °C, 24 h (72–90%).

Interestingly, the same concept involving a catalyst-directing group also facilitated the efficient use of 1,3 asymmetric induction. This, of course, is a much more difficult situation, since additional degrees of freedom have to be controlled in the course of the stereochemistry-defining step of the hydroformylation reaction. However, homomethallylic *o*-DPPB esters **13** reacted to give the *anti*-aldehydes **14** as the major diastereomer in selectivities of about 91:9 (Scheme 7).[13] In these cases, the interplay of a preferred substrate conformation and catalyst delivery by a catalyst-directing group form the basis for the diastereoselectivity observed.[13]

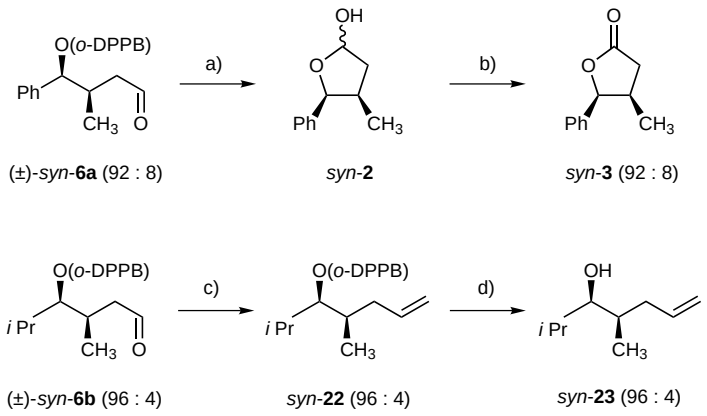
in further skeleton-constructing processes (Scheme 9). In an ideal scenario each reaction would generate the functionality required for a subsequent transformation. Hence, at the end an organic synthesis could be the result in which one reagent-directing group (RDG) would control the selectivity of each single reaction step.

Towards this goal, the potential of the *o*-DPPB group to control diastereoselectivity in a carbon–carbon bond-forming reaction following the hydroformylation step was explored.[15] Enoates **17** were chosen as test substrates since



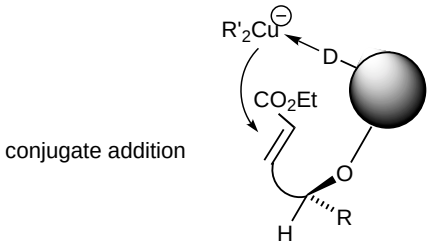
Scheme 9. Multiple use of a reagent-directing group: toward an RDG-controlled organic synthesis.

Removal of the reagent-directing group: After successful hydroformylation one may decide to remove the catalyst-directing *o*-DPPB group. This may be achieved by simple alkaline hydrolysis (*syn*-**6a** →*syn*-**3**)[10] or by hydride reduction after converting the aldehyde, for example, to an alkene by Wittig olefination (*syn*-**6b** →*syn*-**23**) (Scheme 8).[14]



Scheme 8. Reaction conditions: a) KOH, THF/MeOH/H_2O (2:2:1), 50 °C, 2.5 h (99%); b) 2 equiv pyridinium chlorochromate on Al_2O_3, 25 °C, 16 h (95%); c) $Ph_3P{=}CH_2$, THF, −78 →0 °C (89%); d) $LiAlH_4$, diethyl ether, 0 °C (95%).

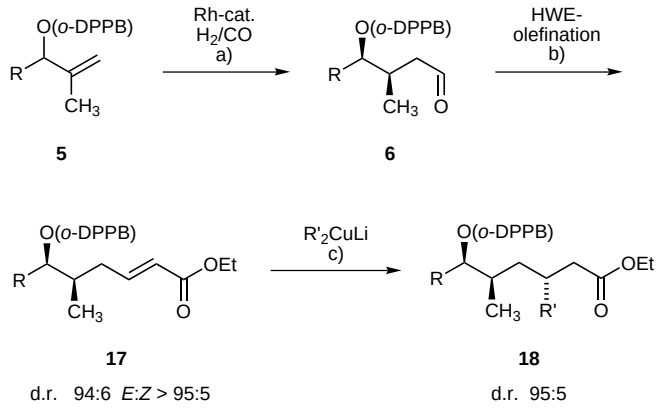
Multiple use of one reagent-directing group: Towards a RDG-controlled organic synthesis: To increase the efficiency of a specifically introduced directing functionality that functionality should be used as often as possible to control selectivity the stereoselective 1,4-addition of a methyl group would provide a structural building block found in biologically important natural products of the polyketide class (e.g. antitumor agent dictyostatin 1 and the ionophore calcimycin) (Scheme 10).



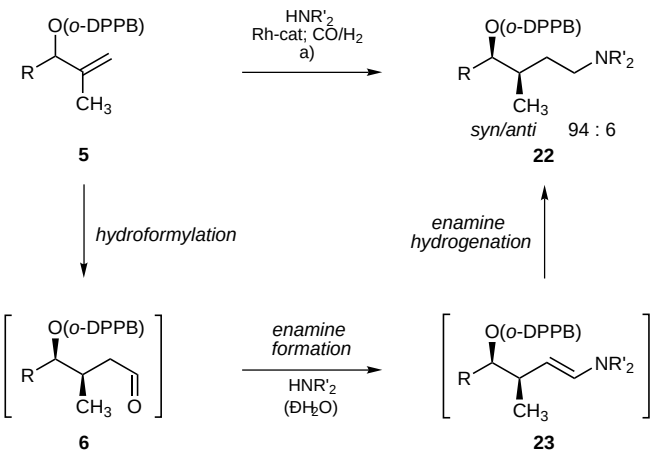
Scheme 10. Working hypothesis for the *o*-DPPB group to act as an organometallic reagent directing group for the conjugate addition of Gilman cuprates to acyclic enoates.

The enoates **17** were obtained in good yield and diastereoselectivity by subjecting the crude hydroformylation products **6** to Horner–Wadsworth–Emmons (HWE) olefination conditions (Scheme 11). Reaction of enoates **17** with dialkyl Gilman cuprates gave the *anti* 1,4-addition product **18** in good yield as the major diastereomer (d.r. $\leq$ 95:5 with respect to the newly formed stereogenic center).[15]

Thus, combining *o*-DPPB-directed hydroformylation with the *o*-DPPB-directed cuprate addition afforded building blocks with up to four stereogenic centers (**19**–**21**). Interestingly 1,4-addition product **21** is equipped with the same

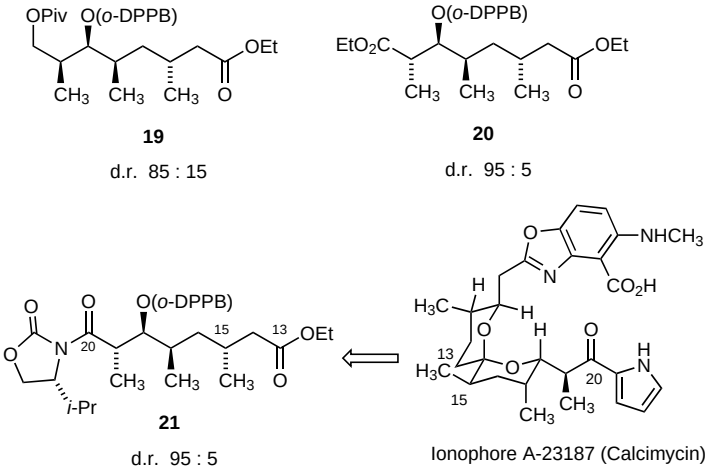


Scheme 11. Reaction conditions: a) 0.7 mol% $[Rh(CO)_2(acac)]$, 2.8 mol% $[P(OPh)_3]$, 20 bar H_2/CO (1:1), toluene, 90 °C; b) $(EtO)_2(O)PCH_2CO_2Et$, *n*BuLi, DME, 20 °C (71–83% both steps); c) 1.5 equiv R′2CuLi, diethyl ether, −78 →0 °C (61–93%).



Scheme 12. Reaction conditions: a) 1.5 equiv HNR'_2, 0.7 mol% $[Rh(CO)_2(acac)]$, 2.8 mol% $[P(OPh)_3]$, 20 →80 bar H_2/CO (1:1), toluene, 90 →120 °C (40–65%).

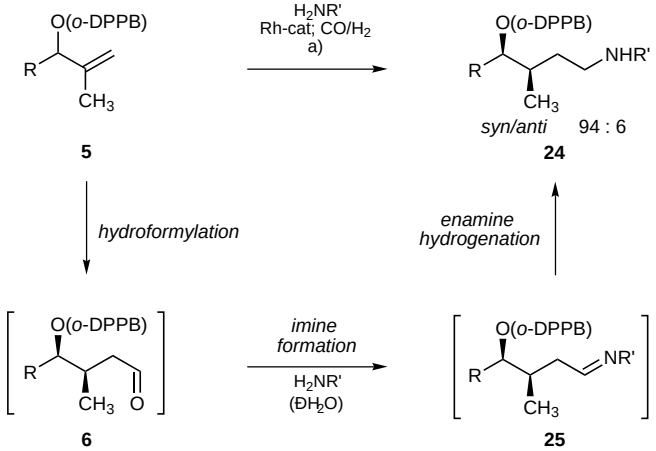
relative and absolute configuration of the four stereogenic centers found in the ionophore calcimycin.



***o*-DPPB-directed hydroformylation as part of sequential transformations**: One may improve efficiency of an *o*-DPPB-directed hydroformylation by incorporating this reaction into sequential transformations (domino reactions).[16] The hydroformylation reaction itself should be ideally suited for such a purpose, since this reaction provides access under fairly mild reaction conditions to the synthetically valuable aldehyde functionality. The aldehyde itself should be ideally suited to allow further skeleton-constructing reactions. One sequential transformation that employs the hydroformylation reaction as a key step is the hydroaminomethylation of olefins originally discovered by Reppe.[17] However, efficient control of diastereoselectivity in the course of this hydroaminomethylation reaction was unknown.[18, 19]

By employing the same concept and the catalyst-directing *o*-DPPB group enabled the development of a substrate-directed diastereoselective hydroaminomethylation of acyclic methallylic alcohol derivatives **5** to give the corresponding amines **22** in diastereoselectivities of greater 94:6 (Scheme 12).[20] This process allows, in one step, the formation of a C–C bond and a C–heteroatom bond, introduction of the ubiquitous amine functionality, and, additionally, generation of a new stereogenic center with high levels of acyclic stereocontrol. The mechanism of this sequential transformation involves presumably three steps. First *o*-DPPB-directed stereoselective hydroformylation of the methallylic *o*-DPPB esters **5** provides the aldehyde **6**. Enamine formation (→**23**) with the secondary amine present and subsequent rhodium-catalyzed hydrogenation finishes the sequence of reactions, and affords the saturated amines **22**.

In addition to secondary amines, primary amines could be employed. These reactions furnished the corresponding secondary amine derivatives as the final products in equally high diastereoselectivity (Scheme 13). In these cases, the reaction sequence must have proceeded through an imine



Scheme 13. Reaction conditions: a) 1.5 equiv H_2NR', 0.7 mol% $[Rh(CO)_2(acac)]$, 2.8 mol% $[P(OPh)_3]$, 20→80 bar H_2/CO (1:1), toluene, 90→120 °C (40–46%).

intermediate **25** followed by a rhodium catalyzed imine reduction. This appeared surprising since previous attempts at hydroaminomethylation starting from primary amines and alkenes by employing similar rhodium catalysts under similar reaction conditions were found to stop generally at the stage of the imine.[21] Hence, a special situation may be given for *o*-

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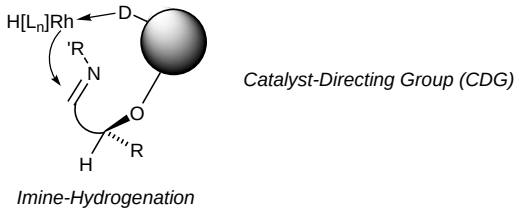
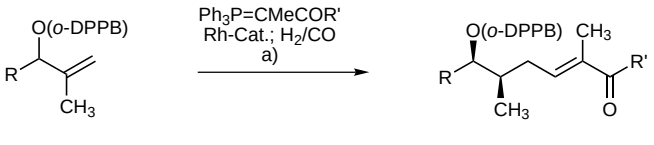
DPPB derivatives **5**. A plausible explanation for the increased reactivity towards imine hydrogenation may take into account the presence of the catalyst-directing *o*-DPPB group (Scheme 14). Thus, it is likely that after imine formation a second catalyst precoordination occurs and an intramolecular imine hydrogenation takes place. Such an intramolecular process should be kinetically favored over a corresponding intermolecular reaction pathway. Hence, the catalyst-directing *o*-DPPB group may be acting within one sequential transformation in two different ways. First, the CDG controls the diastereoselectivity in the hydroformylation step and second it controls the chemoselectivity in the course of the imine reduction.



Scheme 14. Possible role of the *o*-DPPB group in the course of the imine hydrogenation step.

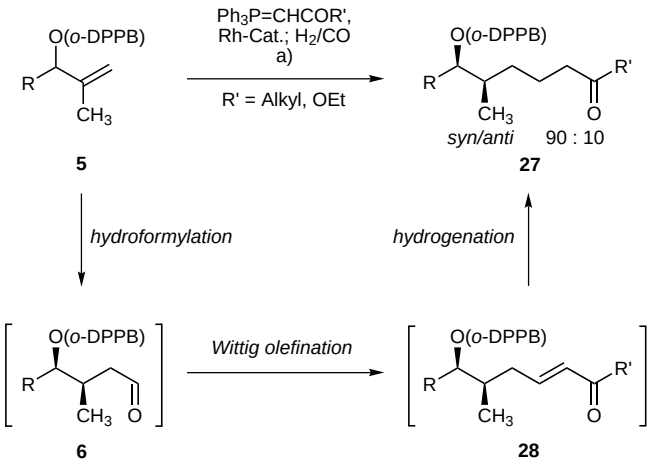
Other sequential transformations that employ the hydroformylation as the key step may be realized if other nucleophiles such as carbon nucleophiles are offered in the course of the hydroformylation reaction. A resulting domino reaction would approach an ideal synthetic method as defined by Hendrickson.[22] Thus, according to his definition, only skeleton-constructing reactions are inevitable and consequently an efficient synthesis should consist only of framework-elaborating steps. Furthermore, if a particular target contains stereogenic centers the most efficient synthetic steps are according to Corey those which in addition to carbon skeleton construction allow the generation of new stereogenic centers selectively.[23] A reaction in agreement with these efficiency criteria would be a domino stereoselective–hydroformylation–Wittig olefination process. This would require that the hydroformylation reaction be compatible with the presence of a Wittig ylide throughout the course of the reaction.

Reacting methallylic and homomethallylic alkenic substrates under hydroformylation conditions in the presence of stabilized Wittig ylides gave the corresponding domino hydroformylation products **26** in good yields and diastereoselectivities (Scheme 15).[24] Whereas in the case of the



Scheme 15. Reaction conditions: a) 1.1 equiv $Ph_3P{=}CMeCOR'$, 0.7 mol% $[Rh(CO)_2(acac)]$, 2.8 mol% $[P(OPh)_3]$, 20 bar H_2/CO (1:1), toluene, 90 °C (60–78%). R′=Me, OEt.

disubstituted stabilized Wittig ylides the reaction stopped at the stage of the trisubstituted olefin **26**, in the case of monosubstituted ylides a further hydrogenation reaction of the α,β-unsaturated carbonyl functionalities occurred and provided the corresponding saturated derivatives **27** (Scheme 16). Control of the diastereoselectivity was provided by the catalyst-directing *o*-DPPB group, which made use of both 1,2- and 1,3-asymmetric induction.



Scheme 16. Reaction conditions: a) 1.5 equiv $Ph_3P{=}CMeCOR'$, 0.7 mol% $[Rh(CO)_2(acac)]$, 2.8 mol% $[P(OPh)_3]$, 20 bar H_2/CO (1:1), toluene, 90 °C (60–82%). R′=Me, OEt.

This domino reaction enables the construction of two carbon–carbon single bonds in one step and additionally generates a new stereogenic center with high levels of acyclic stereocontrol. Through the substituents R and R′ this domino reaction may potentially be used as a fragment-coupling step in the course of a convergent synthetic strategy.

Conclusion

The introduction of an appropriately designed reagent-directing group (RDG) allowed the development of a substrate-directed, stereoselective hydroformylation reaction of acyclic methallylic and homomethallylic alcohol derivatives. The potentially multifunctional character of the introduced reagent-directing *o*-DPPB group was explored in the course of a stereoselective addition of Gilman cuprates to acyclic enoates. Thus, by combining both *o*-DPPB-directed hydroformylation and *o*-DPPB-directed cuprate addition a short and efficient synthesis of the building blocks for polyketide synthesis was devised. Incorporating the *o*-DPPB-directed hydroformylation reaction as part of sequential transformations allowed a further increase of synthetic efficiency.

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