Substrate directed diastereoselective hydroformylation of acyclic homomethallylic alcohols

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Diastereoselective hydroformylation of acyclic homomethallylic alcohols with the aid of a catalyst directing group is achieved and the stereochemical outcome of this reaction is rationalized by analysing the preferred substrate conformation in solution.

Transition metal catalysed C–C bond forming reactions provide efficient ways to build carbon backbones in organic synthesis. These reactions also allow the generation of stereogenic centres, be it with the aid of a chiral catalyst[1] or by substrate based asymmetric induction.[2] The latter approach is not frequently utilized,[3] but its potential may be enhanced by the introduction of a catalyst directing group, a group that binds reversibly to the catalytically active metal species, and positions it selectively at one of the diastereotopic faces of the substrate.[4,5]

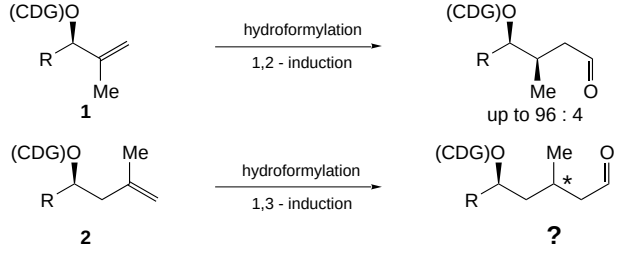
We recently found that *o*-diphenylphosphinobenzoic acid may be used as an effective catalyst directing group in stereoselective hydroformylation of methallylic alcohols **1** (Scheme 1).[5] In this process high 1,2-asymmetric induction is realized by means of the catalyst directing group. We report now that this approach allows also for high 1,3-asymmetric induction in the hydroformylation of homomethallylic alcohols **2** by use of the same catalyst directing group.

To probe 1,3-asymmetric induction homomethallylic alcohols seemed to be particularly interesting substrates, because hydroformylation delivers an acyclic structural fragment with hydroxy and methyl substituted stereocentres in a 1,3 relation. Such a structural motif is widespread, especially in polyketide natural products, and therefore of significant synthetic importance.[6]

Starting from readily available homomethallylic alcohols[7] we introduced the catalyst directing *o*-DPPB group employing the DCC–DMAP coupling method.[8] The resulting homomethallylic *o*-DPPB esters **3** were subjected to hydroformylation conditions using 0.7 mol% of $Rh(CO)_2acac$–$P(OPh)_3$ as the catalyst. The hydroformylation proceeded smoothly to give the corresponding aldehydes **4** in good to excellent yields and with *anti*-diastereoselectivities of up to 91%.†‡

Interestingly a significant dependence of the diastereoselectivity on the reaction temperature was observed. Thus the isopropyl derivative **3a** at 90 °C gave only a 70 : 30 ratio (entry 3). Lowering the reaction temperature to 70 °C and even further to 50 °C improved the diastereomeric ratio from 87 : 13 to 91 : 9 favouring the *anti*-aldehyde (entries 1 and 2). Furthermore no significant influence of the diastereoselectivity on the nature of the substituent R could be detected. Thus primary and secondary alkyl as well as aryl substituents were tolerated and gave diastereomer ratios independant on the nature of R of *ca.* 91 : 9. Remarkable is the hydroformylation of the alkenyl substituted derivative **3f**, in which a 1,1-disubstituted alkene could be reacted chemo-, regio- and stereo-selectively in the presence of a trisubstituted alkene to give the *anti*-aldehyde **4f** in 85% yield and a diastereomeric ratio of 90 : 10 (entry 8).

The observed independence of the diastereoselectivity on the nature of the substituent R seemed to indicate that a conformational preference inherent to the homomethallylic system itself might be the origin of the observed 1,3 asymmetric induction. To test this hypothesis we examined the preferred conformation of the homomethallylic *o*-DPPB ester substrate **3a** in solution at 25 °C. Determination of coupling constants as well as 2D-NOESY spectra showed compound **3a** to have a preferred conformation **A** (Scheme 3) in agreement with MM3 calculations. The driving force for this conformation is the minimization of 1,3-allylic strain and the avoiding of *syn*-pentane interactions.[9] If we assume a coordination of the rhodium catalyst between the catalyst directing group and the alkene as indicated (Scheme 3), hydroformylation would provide the

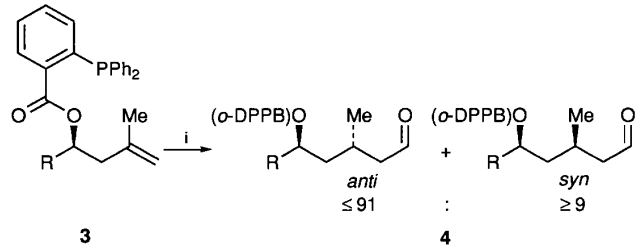


Scheme 1 CDG = Catalyst directing group

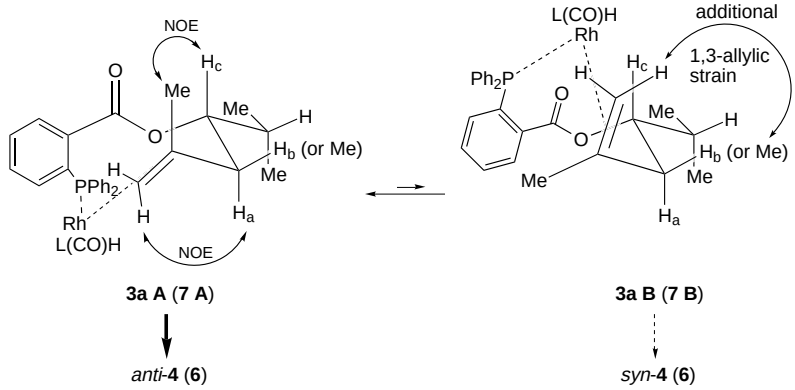
Table 1 Results of the diastereoselective hydroformylation of homomethallylic *o*-DPPB esters **3**

Entry[a]	Compound **3**	R	*T*/°C	*t*/h	Yield (%)[b]	*anti* : *syn*[c]
1	**a**	Pr^i	50	72	93	91 : 9
2	**a**	Pr^i	70	24	99	87 : 13
3	**a**	Pr^i	90	24	99	70 : 30
4	**b**	*c*-Hex	50	72	90	91 : 9
5	**c**	Hex	30	168	81	90 : 10
6	**d**	Ph	30	120	72	90 : 10
7	**e**	*o*-$MeOC_6H_4$	30	240	78	90 : 10
8	**f**	(*E*)-EtCH=CMe	30	168	85	90 : 10

[a] For a general experimental procedure see ref. 5. [b] Isolated yields after column chromatography. [c] Determined by NMR spectroscopy of the crude reaction mixture.



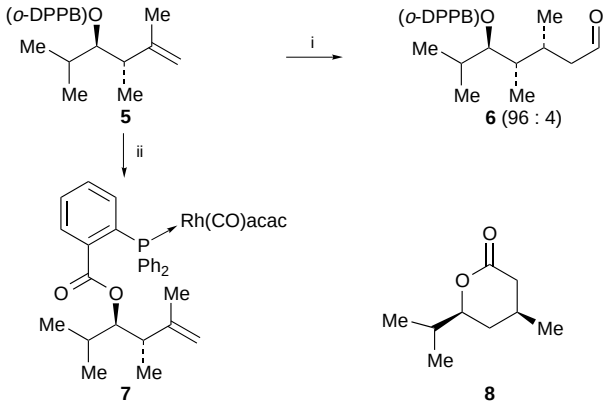
Scheme 2 *Reagents and conditions*: i, 0.7 mol% [$Rh(CO)_2acac$/4 $P(OPh)_3$], 20 bar H_2–CO (1 : 1), toluene, *o*-DPPB = *ortho*-diphenylphosphinobenzoate



3a A (**7 A**) **3a B** (**7 B**)

anti-**4** (**6**) *syn*-**4** (**6**)

Scheme 3 Preferred conformation for **3a** and **7** in $CDCl_3$ solution at 25 °C determined by 2D-NOESY NMR spectra and selective ^1H NMR decoupling experiments. The indicated coordination of the rhodium catalyst to phosphine and alkene is hypothetic.



Scheme 4 *Reagents and conditions*: i, 0.7 mol% $[Rh(CO)_2acac/4\ P(OPh)_3]$, 20 bar H_2–CO (1 : 1), toluene, 50 °C, 7 d, 91%; ii, $Rh(CO)_2acac$, benzene, 25 °C, 15 min, 99%

anti-aldehyde **4** as was found experimentally. The less preferred conformation **B** should give rise to complexation of the opposite diastereotopic alkene face, *i.e.* to the formation of the corresponding *syn*-aldehyde **4**.§

Consequently the replacement of H_b in **3a** by a methyl substituent should favour conformation **A** even more, because the alternative conformation **B** would develop, in addition to the *syn*-pentane interaction between the alkenic methyl substituent and the oxygen substituent, a repulsive 1,3-allylic strain between the additional methyl substituent and the sp^2-hybridized CH_2-fragment. To investigate such a conformational situation as close as possible to hydroformylation catalysis, we prepared the rhodium complex **7** by reacting alcohol **5** with stoichiometric amounts of $Rh(CO)_2acac$. 2D-NOESY and selective proton decoupling experiments showed rhodium complex **7** to have preferentially the conformation **A** at 25 °C in $CDCl_3$ (Scheme 3).

When **5** was hydroformylated at 50 °C, the *anti*-aldehyde **6** was obtained in 91% yield with a diastereomeric ratio of 96 : 4 (Scheme 4). Thus the additional methyl substituent, which disfavours conformer **B**, gives rise to a significantly higher diastereoselectivity in agreement with our model.

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Footnotes

† For a general procedure see ref. 5.

‡ All compounds were characterized by NMR spectroscopy and elemental analyses. The relative stereochemistry was assigned for **4a** by transformation to the known lactone **8** (ref. 10).

§ On going from 30 to 90 °C the vicinal coupling constants for H_aH_c and H_bH_c change from 9.0/4.1 Hz to 8.4/4.6 Hz. These data indicate a change in conformer populations for **3a** when going to the higher temperatures, which is reflected in the temperature dependence of the diastereoselectivities of the hydroformylation reaction.

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