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Directed regio- and stereoselective hydroformylation of mono- and 1,3-disubstituted allylic alcohols: a catalytic approach to the *anti*-aldol-retron†

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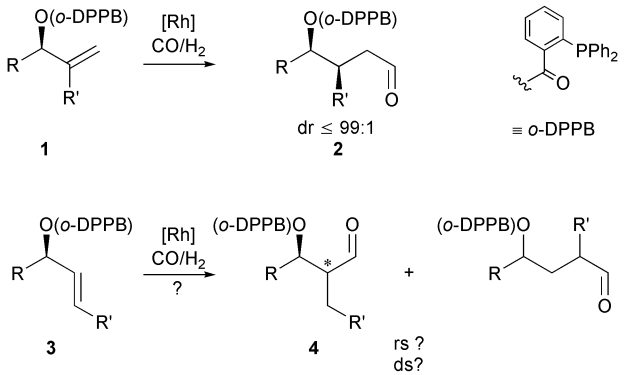
Regioselective and diastereoselective hydroformylation of mono- and 1,3-disubstituted allylic alcohol *o*-DPPB esters is described. The products represent synthetically important *anti*-aldol retrons.

Hydroformylation of alkenes belongs to the most important industrially applied processes relying on homogenous catalysis.[1] However, control of stereochemistry in the course of this reaction is still a challenge.[2] We[3] and others[4] recently introduced a solution to this problem which employs substrate bound catalyst-directing groups. For instance, with the *ortho*-diphenylphosphanylbenzoate function (*o*-DPPB) as the catalyst-directing group we were able to achieve efficient acyclic stereocontrol upon hydroformylation of 1,2-disubstituted allylic alcohol derivatives **1** to give the *syn*-aldehydes **2**.[5] These are interesting building blocks for polyketide synthesis.[6] However, to become a synthetically flexible method a similar approach to an *anti*-stereochemical relation between controlling and newly formed stereogenic center was certainly in demand.

We herein report on the first regio- and diastereoselective hydroformylation of 1,3-disubstituted allylic alcohol derivatives **3** (R′ = Me) with the aid of the catalyst-directing *o*-DPPB group. Extension of this methodology towards hydroformylation of monosubstituted allylic alcohols **3** (R′ = H) is also described.



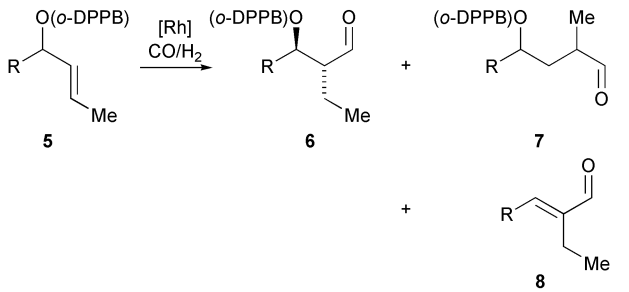
In the course of the hydroformylation of an allylic alcohol derivative **3** two selectivity issues appear, regio- and diastereoselectivity, which have to be controlled simultanously.

We were pleased to find that hydroformylation of allylic *o*-DPPB ester **5** (R = Bn) proceeded smoothly at 30 °C and 20 bar syngas pressure with a rhodium catalyst loading of 0.7 mol% to give the *anti*-aldehyde **6** as the major product in good regio- and diastereoselectivity‡ (Table 1, entry 1). However, the reaction rate was too low. Increasing the catalyst loading to 1.2 mol% reduced the reaction time to 7 d (entry 2). Further improvement was achieved when the pressure was increased to 30 and finally 40 bars (entries 3–5). However, going to higher reaction temperatures resulted in a significantly reduced diastereoselectivity (entry 6) and gave a significant amount of the undesired elimination product **8**. Hence, best results were achieved employing 1.8 mol% catalyst loading, 40 bar syngas and 30 °C in toluene for about 44 h (Table 1, entry 5). These conditions allowed a 90% conversion of *o*-DPPB ester **5** to furnish *anti*-aldehyde **6** in a regioselectivity (**6** : **7**) of 90 : 10 and a diastereomer ratio (*anti*-**6** : *syn*-**6**) of 98 : 2.

Table 1 Dependence of chemo-, regio- and diastereoselectivity of the *o*-DPPB-directed hydroformylation of allylic ester **5** (R = Bn) on reaction conditions

Entry	[Rh][a] (mol%)	$p_{CO/H2}$/ bar	*T*/°C	Time	Conv.[b,c] (%)	**8**[b] (%)	rs[b] (**6** : **7**)	dr (**6**)[b] (*anti* : *syn*)
1	0.7	20	30	13 d	83	5	87 : 13	89 : 11
2	1.2	20	30	7 d	90	7	90 : 10	93 : 7
3	1.2	30	30	4 d	89	< 2	90 : 10	98 : 2
4	2.0	30	30	47 h	92	< 2	89 : 11	94 : 6
5	**1.8**	**40**	**30**	**44 h**	**90**	**< 2**	**90 : 10**	**98 : 2**
6	2.0	40	40	46 h	90	10	89 : 11	90 : 10
7	2.0	40	20	48 h	88	< 2	90 : 10	98 : 2

[a] [Rh] = [Rh(CO)$_2$acac]/1.67 P(OPh)$_3$. [b] Determined from NMR analysis of the crude reaction product. [c] Chemoselectivity towards aldehyde formation was 100% in all cases.



With these optimized conditions in hand we looked at the dependence of the selectivity parameters as a function of the nature of the substituent R at the controlling stereogenic center. Thus, excellent diastereoselectivity was obtained for primary alkyl substituents (Table 2, entries 1, 2, 4). Somewhat reduced diastereoselectivities were noted for secondary alkyl substituents (entries 5, 6), whereas regioselectivity stays in most cases in the order of 9 : 1. However, for an isopropyl-substituted derivative the best regioselectivity (98 : 2, entry 5) was observed.

In order to learn about the influence of double bond geometry on the regio- and stereochemical outcome of the title reaction we studied hydroformylation of *cis*-configured allylic-*o*-DPPB ester **5** (R = Bn). Surprisingly, chemo-, regio- and diastereoselectivity were significantly lower compared to the *trans*-alkenic system **5** (see Table 2, entries 2 and 3).

Interestingly, when monosubstituted allylic *o*-DPPB esters were used a similar regio- and stereodirecting effect of the catalyst-directing *o*-DPPB group was observed (Scheme 1, Table 3). Thus, regioselectivities up to 86 : 14 (**10** : **11**) and diastereoselectivities‡ up to 95 : 5 (*anti*-**10** : *syn*-**10**) were found (Table 3) with formation

† Electronic supplementary information (ESI) available: experimental. See http://www.rsc.org/suppdata/cc/b3/b311378g/

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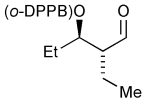
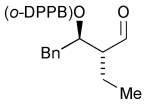
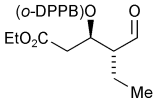
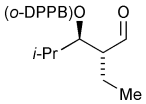
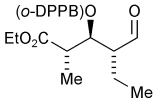
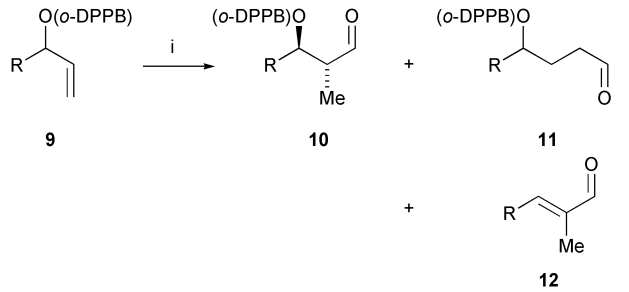
Table 2 Dependence of chemo-, regio- and diastereoselectivity of the *o*-DPPB-directed hydroformylation of allylic esters **5** on substrate structure

Entry	Major product	Conv.[a,b] (%)	**8**[a] (%)	rs[a] (**6** : **7**)	dr (**6**)[a] (*anti* : *syn*)
1		90	3	91 : 9	95 : 5
2		90	< 2	90 : 10	98 : 2
3	from *cis*-**5** (R = Bn)	40	39	61 : 39	58 : 42
4		90	5	92 : 8	92 : 8
5		91	3	98 : 2	87 : 13
6		95	7	90 : 10	91 : 9

[a] Determined from NMR analysis of the crude reaction product. [b] Chemoselectivity towards aldehyde formation was 100% in all cases.



9 **10** **11** **12**

Scheme 1 Conditions: (i) 1.8 mol% $[Rh(CO)_2acac]$, 3 mol% $P(OPh)_3$, H_2/CO (1 : 1) 40 bar, toluene, 30 °C, 46 h.

of the *anti*-aldol retron **10** as the major product. Interestingly, aldehyde **10** represents a potentially valuable building block for the synthesis of polypropionates.

In conclusion, *o*-DPPB-directed regio- and diastereoselective hydroformylation of 1,3-disubstituted and mono-substituted allylic *o*-DPPB esters **3** could be achieved. This methodology gives access to the *anti*-aldol retron which is difficult to reach through aldol chemistry directly. Thus, directed hydroformylation may become a synthetically attractive alternative to established aldol[7] or allylmetal[8] chemistry for the construction of *anti*-aldol retron type products.

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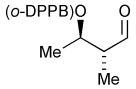
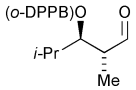
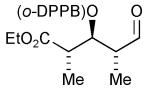
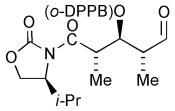
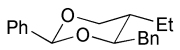
Table 3 Regio- and diastereoselectivity for *o*-DPPB-directed hydroformylation of mono-substituted allylic esters **9**

Entry	Major product	Conv.[a,b] (%)	**12**[a] (%)	rs[a] (**10** : **11**)	dr (**10**)[a] (*anti* : *syn*)
1		> 97	5	64 : 36	91 : 9
2		90	3	86 : 14	95 : 5
3		90	8	83 : 17	86 : 14
4		92	19	84 : 16	88 : 12

[a] See footnotes *a*, *b* in Table 2. [b] See footnotes *a*, *b* in Table 2.

Notes and references

‡ The *anti*-stereochemical relation of **6** (R = Bn) and **10** (R = *i*-Pr) could be determined upon chemical transformation into the benzylidene acetals **13** and **14**, respectively, employing the following reaction sequence: i $LiAlH_4$, ether, 0 °C; ii $PhCH(OMe)_2$, TsOH cat., CH_2Cl_2, rt. Inspection of coupling constants as well as NOESY data allowed assignment of relative configuration.



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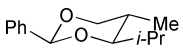

14

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