Hydroformylation

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An Asymmetric Hydroformylation Catalyst that Delivers Branched Aldehydes from Alkyl Alkenes**

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Enantioselective hydroformylation of alkenes can simultaneously create a new C–C bond, install a very versatile functional group, and produces enantiomerically enriched compounds from very economic reagents: an alkene, carbon monoxide, and hydrogen. Given the precedent for large-scale production of achiral linear aldehydes, hydroformylation can be viewed as potentially the ideal reaction for commercial production of chiral building blocks.[1] However, there have been far more hurdles to overcome relative to core asymmetric production methods such as asymmetric hydrogenation, despite decades of research effort.

After intensive research effort, a range of catalysts that give good enantiomeric excess (*ee*) for model substrates (e.g. styrene) are now available.[2] There is now substantial research and commercial interest in making products of relevance to the pharmaceutical industry and organic synthesis using this technology.[3] Despite all this activity, the control of regioselectivity towards the branched aldehyde is at best only a partially resolved issue. Certain well-known substrates like styrene give the branched aldehyde with a typical regioselectivity of around 10:1, which is usable after purification, although higher selectivity is desirable. Some functionalized substrates show a very high preference for the branched aldehyde with the correct choice of catalyst, and ligands that simultaneously act as reversible auxiliaries for the substrate and bind rhodium have been applied successfully to control regioselectivity for specific functionalized alkenes.[4] A completely unresolved issue that would represent a huge step forward is the controlled formation of branched chiral aldehydes from simple terminal alkyl olefins of type $RCH_2CH{=}CH_2$. Here we show the most significant progress yet towards this general goal, with the first catalytic reactions that combine significant regioselectivity and enantioselectivity for alkenes of type $RCH_2CH{=}CH_2$.

We have had a long-standing interest in obtaining branched aldehydes from alkyl alkenes, but in the absence of any real leads have confined these efforts to screening novel catalysts that were originally designed to solve other problems in carbonylation catalysis. In one recent research project aimed at further tuning the excellent performance of the important asymmetric hydroformylation ligands, Kellihite and Ph-bpe, we considered a hybrid non-symmetric ligand that would present the best of both these ligands, and might gain advantage from being non-C_2 symmetric. Phosphine-phosphites have attracted much interest in hydroformylation,[2g,l–q] although phospholano derivatives or derivatives using a $-CH_2O-$ backbone are not well studied.[2n,p] The ligand, that we have tended to refer to as bobphos ("best of both phosphorus ligands"), (S_{ax},*S*,*S*)-**4**, can be produced reliably by the route shown in Scheme 1 from the known precursor **1**.[5] The phosphite coupling was accomplished by activating (*S*)-**2** with Me_3SiI; this does not proceed cleanly and the ca. 40:60 mixture of iodide (*S*)-**3** and (*S*)-**2** was reacted directly with the known precursor **1** in the presence of DABCO as base and deprotecting agent to give, after purification, (S_{ax},*S*,*S*)-**4**.[5] (R_{ax},*S*,*S*)-**4** was also prepared from (*R*)-**2**.

This ligand was initially examined in the hydroformylation of the model substrate, vinyl acetate (Scheme 2). Bobphos delivered $>99\%$ conversion to aldehyde after 4 h at 2.5 bar pressure at 60 °C; the linear isomer was observable only in trace quantities (see Supporting Information) and an 83 % *ee* was measured. The other diastereomer of the ligand, (R_{ax},*S*,*S*)-**4** made from the opposite enantiomer of chiral diol, gave 32 % *ee* of the opposite enantiomer of 2-acetoxypropanal (not shown); a classic matched/mismatched scenario for a multiple-stereocenter ligand.

With this encouraging result in hand, we considered the use of bobphos in hydroformylations of alkenes of type $RCH_2CH{=}CH_2$. Due to high demand in the commodity chemicals industry for linear alkyl aldehydes, an extremely large set of ligands has been tested in the hydroformylation of substrates such as hex-1-ene. Almost without exception, the linear aldehyde is produced preferentially, with some ligands delivering exquisite linear selectivity.[1] A couple of examples where branched aldehydes are formed in preference to linear product are not enantioselective.[6] An example where a chiral ligand was examined in this class of alkenes was an interesting study by Nozaki and co-workers using the important binaphos ligand; enantioselective hydroformylation of hex-1-ene gave good enantioselectivity, but the undesired linear aldehyde was more than 75 % of the product mix ($b{:}l = 1{:}3.0$).[7] It was therefore with meagre expectations that we tested bobphos in a selection of hydroformylations of alkenes of type $RCH_2CH{=}CH_2$ (Scheme 3 and Tables 1 and 2).

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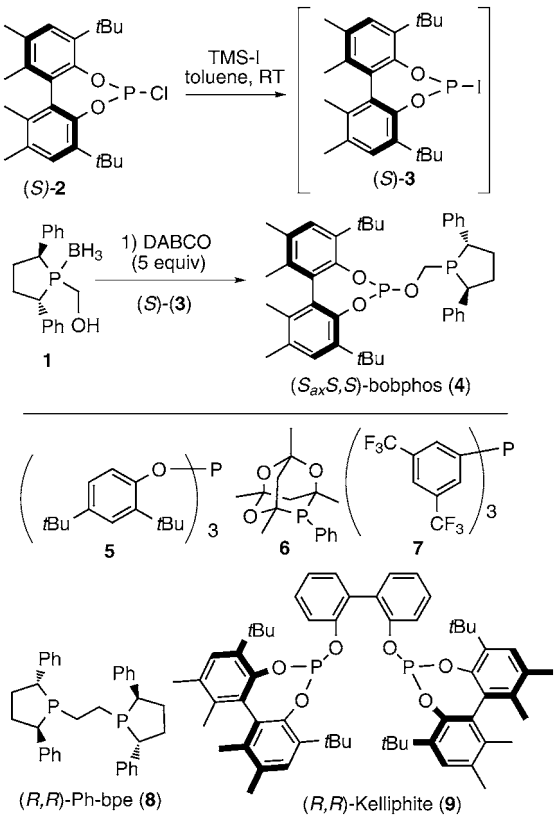
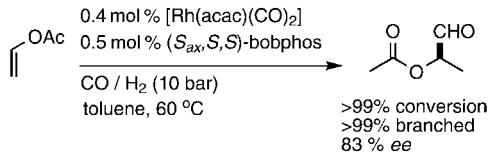
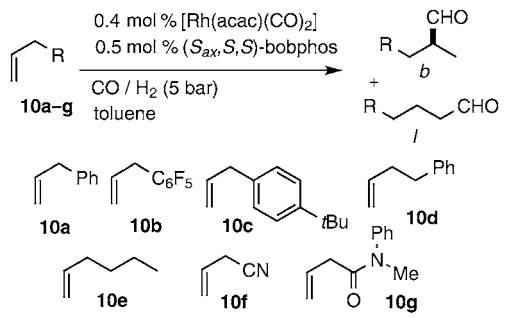


Scheme 1. Synthesis of "bobphos" and numbering scheme for other ligands used in this study. DABCO = 1,4-diazabicyclo[2.2.2]octane.



Scheme 2. Enantioselective hydroformylation of vinyl acetate can be accomplished by using Rh/bobphos catalyst.

The results are, to say the least, rather surprising. Table 1 shows hydroformylation of allyl benzene (**10a**) using a variety of phosphine ligands known to be proficient in hydroformylation. Unusually, these studies were carried out at temperatures as low as 15 °C, since our studies have shown that this



Scheme 3. Enantioselective hydroformylation of alkenes of type $RCH_2CH{=}CH_2$.

Table 1: Hydroformylation of allyl benzene (**10a**) using a range of hydroformylation catalysts at room temperature.

Entry[a]	Ligand	Product yield [%][b]	*b:l*[b]	*ee*[c]
1	Ph_3P	46	1:1.1	n.d.
2	**5**	86	1:1.2	n.d.
3	**6**	91	1:1.1	n.d.
4	**7**	93	1:1.8	n.d.
5	dppe[d]	56	1:1.0	n.d.
6	dppf[d]	52	1:1.2	n.d.
7	**8**	66	1:1.1	0
8	**9**	87	1:1.0	5
9	**4**	64[e]	4.0:1	90
10	**4**	39[f]	3.6:1	88

[a] 0.4 mol % $[Rh(acac)(CO)_2]$ and 0.5 mol % bidentate ligand or 1.2 mol % monodentate ligand were stirred at 5 bar syngas at 50 °C for 40 min in toluene (2 mL), prior to running reactions at 16 °C at 5 bar initial syngas pressure for 3 days. [b] % Product determined by ^{1}H NMR spectroscopy using Et_4Si as internal standard. [c] Determined by HPLC analysis of the alcohol formed after reduction with $NaBH_4$. [d] dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1′-bis(diphenylphosphino)ferrocene. [e] 53 % yield of the corresponding alcohol over two steps after purification. [f] Reaction time of 4 h at 30 °C.

favors the formation of the branched aldehyde. All catalysts were pre-formed under a syngas atmosphere at 50 °C since this is advisable if hydroformylations are to be attempted under such mild conditions. All the established ligands are unselective or show a slight preference towards the linear aldehyde. In contrast, bobphos gives 80 % selectivity in favor of the branched aldehyde (Table 1, entry 9: only 2-methyl-3-phenylpropanal and linear 4-phenylbutanal were detected). Moreover, control of enantioselectivity is also possible with 90 % *ee* in favor of the (*S*) enantiomer observed at room temperature. Another surprising result is that Kelliphite and Ph-bpe, the ligands from which bobphos is derived from, give no enantioselectivity in these reactions; a result we have triple checked and have no explanation for, although we note that most hybrid ligands made from two very successful ligands perform worse than the parent ligands, while in this case the hybrid is of two ligands that are very poor for this substrate!

We have tested a range of other substrates that should be linear selective; in order to prepare racemic standards for analytical development, all of these substrates were examined using ligand **6**, previously one of the few ligands to favor branched aldehyde formation to some degree and this generally gave moderate selectivity towards the linear aldehyde (see Supporting Information). By using the new (S_{ax},*S*,*S*)-bobphos catalyst system, we have observed preferential formation of the branched aldehyde for the first time, and with high enantioselectivity for the (*S*) isomer.

In the reactions in Table 2, we have generally used quite long reaction times and unusually low temperatures to maximize *ee*, but as shown (Table 2, entries 2 and 3), a slight increase in temperature enables the conversion of **10b** into products in a few hours with very similar results. In addition to opening up the prospect of a general, practical branched-selective hydroformylation methodology in the future, the ready availability of simple alkenes means that, depending on the ability to purify products downstream, this catalyst may

Table 2: Hydroformylation of alkenes of type $RCH_2CH{=}CH_2$ using Rh/bobphos catalyst, (S_{ax},*S*,*S*)-**4**.

Entry[a]	Substrate	*T* [°C]	Conv. [%][b]	Product yield [%][b,d]	*t* [h]	*b*:*l* [b]	*ee*[c]
1	**10b**	16	81	81	21	6.2:1	91
2	**10b**	30	75	75	8	5.4:1	89
3	**10b**	40	90	90	4	5.3:1	88
4	**10c**	16	99	99	66	3.0:1	92
5	**10d**	16	89	89	70	2.5:1	75
6	**10e**	16	78	70	46	3.0:1	93
7	**10f**[e]	30	>99	>99	14	10.0:1	81
8	**10f**[e]	60	>99	>99	0.6	8.7:1	71
9	**10g**	16	72	71	29	4.5:1	92

[a] 0.4 mol% [Rh(acac)$(CO)_2$] and 0.5 mol% (S_{ax},*S*,*S*)-**4** were stirred at 5 bar syngas at 50°C in toluene, prior to running reactions at 5 bar initial syngas pressure at temperature and time specified. [b] % Conversion = terminal alkene consumed; % product = linear and branched aldehydes determined by ^{1}H NMR spectroscopy using Et_4Si as internal standard (only two aldehydes detected in each case). [c] See Supporting Information for analytical methods. [d] All products were isolated and purified after reduction with $NaBH_4$; see Supporting Information. [e] 10 bar initial pressure.

already be practical. For example, aldehydes of general formula ArCHCH(CHO)Me are of importance to the fragrance industry, with lillial being one of the most important of these at present. Lillial is the product formed from branched-selective hydroformylation of simple alkene **10c**. This is considerably more direct than alternative asymmetric syntheses.[8] Whether a single enantiomer is required or not, the alternative procedure reported here delivers significant conversion to lillial in a very direct manner.

There are also commercial products that could be produced from (*S*)-methyl hexanal that require several steps, a procedure starting from very cheap hex-1-ene is potentially very attractive.[9] Using Rh/bobphos gave the branched aldehyde as the major product and with high enantioselectivity (93% *ee*).

Allyl cyanide is a substrate that, while fitting our $RCH_2CH{=}CH_2$ classification, would be expected to deliver the branched isomer with modest regioselectivity;[2c,j] the results obtained with bobphos are amongst the best observed. The other functionalized alkene, **10g**, has not, to the best of our knowledge, been examined before and was hydroformylated with good selectivity to the branched isomer, in contrast to a reaction using a Rh catalyst and ligand **6** that was modestly linear selective (Table 2, entry 9, and see Supporting Information, Table S1). In all the reactions conducted with Rh/bobphos, we have never detected any isomerized alkenes or other branched aldehydes that may result from hydroformylation of the internal alkenes. Given that the catalyst also performs best under conditions that would hinder isomerization, this ligand exerts a strong preference towards branched aldehyde formation from the terminal alkene.

In conclusion, a new phosphine-phosphite ligand has been found to give the branched aldehyde with significant selectivity even in the hydroformylation of alkyl olefins of type $RCH_2CH{=}CH_2$. In addition, it produced these chiral aldehydes with high enantioselectivity. This discovery should open the way towards a significant expansion in the scope of Rh-catalyzed hydroformylation processes.

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