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Chiral Phosphinephosphites Having Axial and Central Chirality in Asymmetric Hydroformylations*

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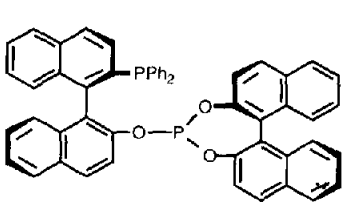
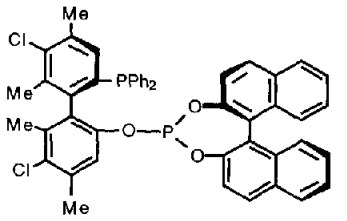
Abstract. Chiral phosphinephosphites were prepared by the reaction of enantiomerically pure *cis*- or *trans*-3-diphenylphosphinotetrahydrofuran-4-ol with atropisomeric chlorophosphites. These ligands were tested in the rhodium catalyzed hydroformylation of allyl acetate. Selectivities up to 44 %*ee* were observed in dependence on the configuration of the applied phosphinephosphites and the bulk of the aromatic groups bound to the phosphorus. The results clearly show that both, central and axial chirality are responsible for the stereochemical outcome of this reaction.

The regio- and enantioselective hydroformylation of prochiral olefines is of considerable chemical[1] and pharmaceutical interest[2]. Much effort has been directed to the application of rhodium or platinum complexes bearing chiral bisphosphines or bisphosphites as ligands.[3] Catalysts with mixed bidentate ligands have been investigated only in a few cases, although there is no doubt about their catalytic potential. In particular, recent publications from the group of Takaya on the utilization of atropisomeric phosphinephosphite-Rh(I) catalysts such as complexes based on (*R,S*)-BINAPHOS[4] or (*R,S*)-BIPHEMPHOS[5] showed their versatility in the highly regioselective and enantioselective hydroformylation.



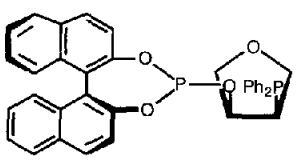
(*R,S*)-BINAPHOS



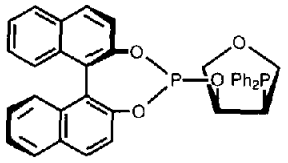
(*R,S*)-BIPHEMPHOS

An interesting feature of this type of catalyst is that the application of the diastereomeric (*R,R*)-ligands resulted in a much lower %*ee*. This observation stresses the importance of the proper choice of the *matched* pair of ligand diastereomers over the *mismatched* constellation.[6] The results obtained with the

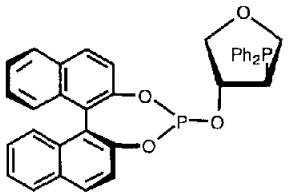
bisatropisomeric systems prompted us to communicate here our observations obtained with Rh-catalysts based on phosphinephosphites (*S*,3*R*,4*S*)-**1**, (*R*,3*R*,4*S*)-**1**, (*S*,3*R*,4*R*)-**2** and (*R*,3*R*,4*R*)-**2**. In contrast to the phosphinephosphites described above, these ligands contain axial as well as central chirality.[7]



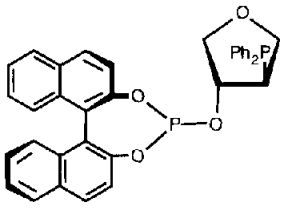
(*S*,3*R*,4*S*)-**1**



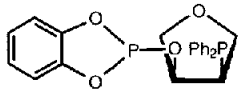
(*R*,3*R*,4*S*)-**1**



(*S*,3*R*,4*R*)-**2**

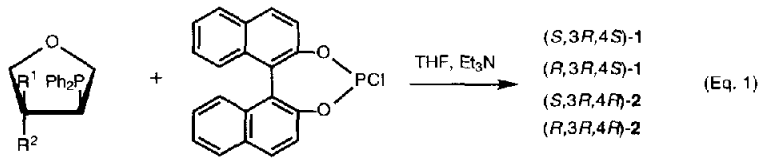


(*R*,3*R*,4*R*)-**2**



(3*R*,4*S*)-**3**

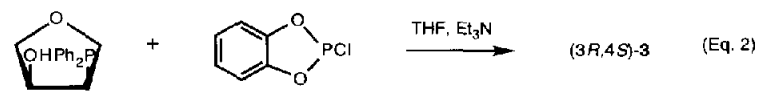
The phosphinephosphites were prepared by the reaction of the enantiopure *cis*- or *trans*-hydroxy phosphines (3*R*,4*S*)-**4** and (3*R*,4*R*)-**5**, easily available from L-ascorbic acid or D-isoascorbic acid,[9] with the atropisomeric chlorophosphites (*S*)-**6** or (*R*)-**6**, respectively, in THF in the presence of triethylamine (Eq. 1).[10] In order to investigate cooperative effects between axial and central chirality the two pairs of diastereomers were synthesized.[11]



(Eq. 1)

(3*R*,4*S*)-**4**: R^1 = OH, R^2 = H
(3*R*,4*R*)-**5**: R^1 = H, R^2 = OH

(*S*)-**6** or (*R*)-**6**



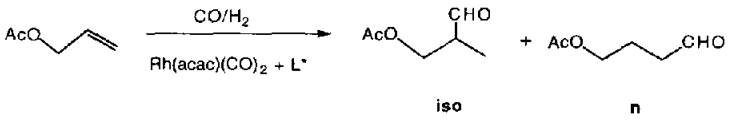
(Eq. 2)

(3*R*,4*S*)-**4**

7

This synthetic approach also allowed the convenient preparation of (3*R*,4*S*)-**3** by the reaction of the hydroxy phosphine (3*R*,4*S*)-**4** with catechol chlorophosphite **7** (Eq. 2).[12] After the work-up using column chromatography, the new ligands could be obtained in an analytically pure form as air-sensitive viscid oils.

Hydroformylation was performed under classical conditions with THF as solvent (Eq. 3). Two modes of preparation of the catalysts were tested, but only one provided for an active catalyst. Thus, treatment of the phosphinephosphites with $Rh(acac)(CO)_2$ gave the corresponding $Rh(P\text{-}P)(CO)_2$-complexes, which could be isolated in good yields. However, these complexes only performed poorly as hydroformylation catalysts. The *in situ* preparation of the catalysts by mixing the ligand with $Rh(acac)(CO)_2$ was revealed to be more advantageous. As a test substrate for the reaction allyl acetate was investigated. Representative results are listed in Table 1.



(Eq. 3)

Table 1. Results obtained in the asymmetric hydroformylation of allyl acetate with phosphinephosphite-Rh-complexes [a]

run	ligand	ratio L*/Rh(acac)(CO)$_2$	conversion [b] (%)	ratio [c] iso/n	%*ee* [d,e] (opt. rot.)
1	(*S*,3*R*,4*S*)-**1**	1/1	90	65/35	9 (+)
2	(*R*,3*R*,4*S*)-**1**	1/1	85	75/25	11 (-)
3	(*S*,3*R*,4*R*)-**2**	1/1	77	5/95	23 (+)
4	(*R*,3*R*,4*R*)-**2**	1/1	78	30/70	12 (+)
5	(3*R*,4*S*)-**3**	1/1	100	70/30	3 (+)
6	(*S*,3*R*,4*S*)-**1**	5/1	100	76/24	32 (+)
7	(*R*,3*R*,4*S*)-**1**	5/1	100	72/28	12 (-)
8	(*S*,3*R*,4*R*)-**2**	5/1	100	64/36	44 (+)
9	(*R*,3*R*,4*R*)-**2**	5/1	97	60/40	14 (+)
10	(3*R*,4*S*)-**3**	5/1	96	50/50	1 (+)

[a] 0.01 or 0.05 mmol chiral ligand, 0.01 mmol $Rh(acac)(CO)_2$, 1 mmol substrate, 15 ml THF, 40 bar of syn gas (CO/H_2 = 1/1 molar ratio) at 80 °C. [b] after 15 h. [c] determined by GC on OV 101. [d] determined on Lipodex E. [e] The addition of ethyl orthoformate did not significantly improve the %*ee*.

In runs 1-5 equimolar ratios of ligand and $Rh(acac)(CO)_2$ were employed. With the exception of run 3 and 4 moderate or good regioselectivities in favour of the branched aldehyde were achieved. Under the conditions applied for the atropisomeric ligands a change of the regioselectivity in favour of the linear product with increasing reaction time was observed. The highest %*ee* in the 1/1-series have been obtained with the ligand bearing the (*S*)-configurated 1,1'-binaphthyl core (*S*,3*R*,4*R*)-**2** (run 3). All catalysts containing the ligands with

the binaphthalene moiety performed superior to the complex based on the catechol ligand *(3R,4S)*-**3** (run 5 and 10). These results clearly demonstrate that the enantioface discriminating ability of such hydroformylation catalysts is supported by a bulky aromatic moiety. The reaction is sensitive to the ligand/Rh ratio. Thus, time constant and improved regio- and enantioselectivities (particularly for the (*S*)-atropisomers) were obtained by application of the 5-fold amount of phosphinephosphites. Under these conditions (*S,3R,4R)*-**2** yielded, as in run 3, the highest %ee (run 8). Notably, the change from the *cis*-configurated THF-backbone to the corresponding *trans* relationship changed the direction of the chirality induced (runs 2 and 4 or 7 and 9, respectively). This tendency may be counteracted using the (*S*)-configurated binaphthyl moiety (runs 1 and 6). In other words, for the *cis*-phosphinephosphites **1** the influence of the axial chirality to the stereoselectivity is higher than the contribution of the central chirality, whereas in the *trans* series **2** this relation is opposite. For the ligands presented above the (*S,3R,4R*)-relationship is the *matched* pair for the considered reaction.

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* Dedicated to Prof. Dr. Henri Brunner on the occasion of his 60th birthday.

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7 This contribution is part of our engagement in the application of chiral hydroxyalkyl phosphines as ligands or ligand precursors, respectively, in asymmetric catalysis. See ref. 8.

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11 (*S,3R,4S*)-**1**: $[\alpha]_D^{24}$ = +265.7 (*c* 1, $CHCl_3$); ^{31}P-NMR (250 MHz, $CDCl_3$) 144.6, 137.4, -22.8 ppm; $C_{36}H_{28}O_4P_2$; MS (field desorption) 586. (*R,3R,4S*)-**1**: $[\alpha]_D^{24}$ = -331.9 (*c* 1, $CHCl_3$); ^{31}P-NMR (250 MHz, $CDCl_3$) 138.1, -22.0 ppm; $C_{36}H_{28}O_4P_2$; MS (field desorption) 586. (*S,3R,4R*)-**2**: $[\alpha]_D^{32}$ = +214.1 (*c* 1, $CHCl_3$); ^{31}P-NMR (250 MHz, $CDCl_3$) 145.2, 139.3, -12.1 ppm; $C_{36}H_{28}O_4P_2$; MS (field desorption) 586. (*R,3R,4R*)-**2**: $[\alpha]_D^{24}$ = -262.6 (*c* 1, $CHCl_3$); ^{31}P-NMR (250 MHz, $CDCl_3$) 147.8, -12.0 ppm; $C_{36}H_{28}O_4P_2$; MS (field desorption) 586.

12 (*3R,4S*)-**3**: $[\alpha]_D^{33}$ = -47.8 (*c* 1.08, $CHCl_3$); ^{31}P-NMR (250 MHz, $CDCl_3$) 127.2, -22.0 ppm; $C_{22}H_{20}O_4P_2$; MS *m/e* 410 (M^+), 339, 255, 185, 183.

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