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Rh-catalysed asymmetric hydrogenations with a dynamic library of chiral tropos phosphorus-ligands

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Abstract—A library of 16 chiral tropos phosphorus-ligands, based on a chiral P-bound alcohol or secondary amine and a flexible (tropos) P-bound biphenol unit, was synthesised. This ligand library allowed the screening of 16 homocombinations and 115 heterocombinations for the rhodium catalysed asymmetric hydrogenation of methyl *N*-acetamido acrylate. The screening resulted in the identification of a phosphite/phosphoramidite heterocombination, which proved to be extremely effective and enantioselective (100% yield, 94% ee).
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The rhodium catalysed asymmetric hydrogenation of prochiral olefins is a well established methodology for the production of enantiomerically enriched molecules.[1] Chiral bisphosphorus-ligands have played a major role in this reaction since the pioneering work of Knowles and Kagan.[1] Recently, monodentate phosphorus-ligands have experienced a gold rush, allowing for high enantioselectivities, sometimes even better than the bidentate ligands.[2] In particular, readily accessible, inexpensive and highly diverse monodentate ligands such as phosphoramidites, phosphonites and phosphites have been used.[3] An important breakthrough in this area was recently made independently by Reetz et al.[4] and Feringa and co-workers[5] through the use of a mixture of chiral monodentate P-ligands.[6] By mixing two ligands (L^a and L^b) in the presence of Rh, three species are present in various ratios:[7] RhL^aL^a, RhL^bL^b and RhL^aL^b. The heterocombinations allowed for better yields and enantioselectivities when compared to the corresponding homocombinations.[4,5] Usually mixtures of different axially chiral (binaphthol based) monodentate P-ligands were used, but also mixtures of chiral and achiral P-ligands were recently tested with some success.[4c]

Following our longstanding interest in the search for combinatorial approaches to enantioselective catalysis,[8] we became interested in the development of chiral phosphorus-ligands for asymmetric hydrogenation based on a chiral P-bound alcohol or secondary amine and a flexible (tropos)[9] P-bound biphenol unit (Fig. 1). This motif

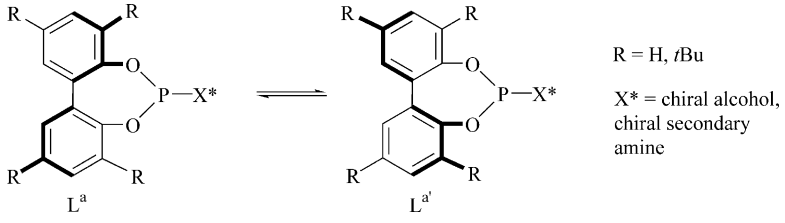

Figure 1. Chiral phosphorus-ligands based on a chiral P-bound alcohol or secondary amine and a flexible (tropos) P-bound biphenol unit.

Keywords: Enantioselective catalysis; Asymmetric hydrogenation; Rhodium; Phosphites; Phosphoramidites.
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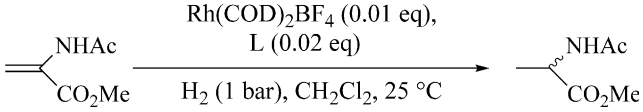
had recently been described by Alexakis and co-workers (phosphoramidite ligands)[10] and Dieguez et al. (bisphosphite ligands)[11] in the enantioselective copper-catalysed conjugate addition of diethylzinc to enones, by Reetz et al. in the Rh-catalysed hydrogenation (bisphosphite ligands),[12] by van Leeuwen and co-workers in the Rh-catalysed hydroformylation reaction (bisphosphite ligands),[13] and by Alexakis and co-workers in the enantioselective copper-catalysed allylic substitution (phosphoramidite ligands).[14] Kondo and co-workers applied the same concept to the asymmetric Grignard cross-coupling reaction, using a phosphorus-ligand based on a chiral amine with a conformationally flexible (tropos) *N*-Ar axis.[15]

Our ligands (Fig. 1) exist, in principle, as a mixture of two interconverting diastereomers, L^a and $L^{a'}$, differing in the conformation of the biphenol unit. Upon complexation with Rh, the ligand (L^a in equilibrium with $L^{a'}$) should give rise to three different species, namely RhL^aL^a, $RhL^aL^{a'}$, $RhL^{a'}L^{a'}$. These three diastereomeric species, which might be interconverting, are generated in proportions, which most likely differ from the statistical value (1:2:1). The novelty of our approach consists in the use of a combination of two of these ligands (L^a in equilibrium with $L^{a'}$ and L^b in equilibrium with $L^{b'}$) resulting in the generation of a dynamic 'in situ' library,[16] with up to 10 different species theoretically present in solution: RhL^aL^a, $RhL^aL^{a'}$, $RhL^{a'}L^{a'}$, RhL^bL^b, $RhL^bL^{b'}$, $RhL^{b'}L^{b'}$, RhL^aL^b, $RhL^aL^{b'}$, $RhL^{a'}L^b$, $RhL^{a'}L^{b'}$. Although each species could, in principle, be present and catalyse the reaction, one of them could overcome the others, determining the direction and the extent of the enantioselectivity.

In this letter, as a proof of the above concept, we present our results on the use of combinations of chiral phosphite and phosphoramidite ligands containing a tropos biphenol unit for the rhodium catalysed asymmetric hydrogenation of methyl *N*-acetamido acrylate.[17–19] A library of 16 ligands, 8 phosphites [$P(O)_2O$ **1**–**8**] and 8 phosphoramidites [$P(O)_2N$ **9**–**16**] (Fig. 2), was synthesised from either commercially available or easily prepared starting materials.[20–25]

Firstly, the chiral ligands were screened individually (homocombinations, Scheme 1, Table 1). In general, phosphites proved to be much more reactive than



Scheme 1.

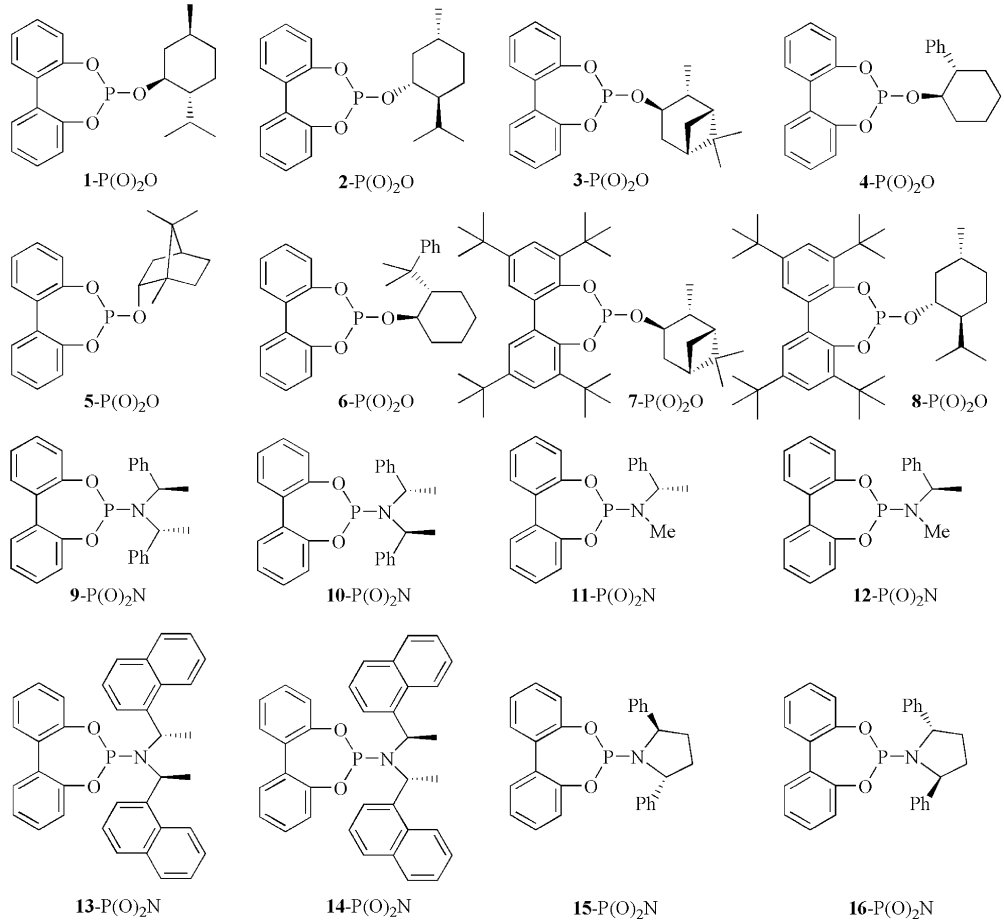


Figure 2. Library of 16 ligands, 8 phosphites [$P(O)_2O$ **1**–**8**] and 8 phosphoramidites [$P(O)_2N$ **9**–**16**].

Table 1. Rhodium catalysed asymmetric hydrogenation of methyl *N*-acetamido acrylate (ligand homocombinations)[a]

Entry	Ligand	Conversion (%)	ee (%)	Absolute configuration
1	**1**-P(O)$_2$O	100	11	*S*
2	**2**-P(O)$_2$O	100	11	*R*
3	**3**-P(O)$_2$O	100	25	*R*
4	**4**-P(O)$_2$O	80	53	*S*
5	**5**-P(O)$_2$O	100	55	*R*
6	**6**-P(O)$_2$O	100	48	*R*
7	**7**-P(O)$_2$O	100	*rac*	—
8	**8**-P(O)$_2$O	100	36	*S*
9	**9**-P(O)$_2$N	7	52	*R*
10	**10**-P(O)$_2$N	7	52	*S*
11	**11**-P(O)$_2$N	100	44	*S*
12	**12**-P(O)$_2$N	100	44	*R*
13	**13**-P(O)$_2$N	15	*rac*	—
14	**14**-P(O)$_2$N	15	*rac*	—
15	**15**-P(O)$_2$N	30	13	*S*
16	**16**-P(O)$_2$N	30	13	*R*

[a] Standard reaction conditions for the library screening (ligand homocombinations): the ligand (0.004 mmol) was weighed and treated at room temperature, under argon, with dry DCM (1.0 mL) and $Rh(COD)_2BF_4$ (0.002 mmol, 0.8 mg). After 45 min, a solution of methyl *N*-acetamido acrylate (0.2 mmol, 28.6 mg) in dry DCM (1.0 mL) was added. The mixture was purged with H_2, and stirred for 60 h. Conversions and ee's were determined by GC equipped with a chiral capillary column (MEGADEX DACTBSβ, diacetyl-*t*-butylsilyl-β-cyclodextrin).

Table 2. Rhodium catalysed asymmetric hydrogenation of methyl *N*-acetamido acrylate (ligand heterocombinations): selected results[a]

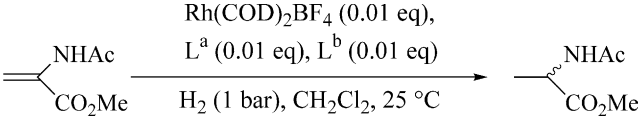
Entry	Ligand L^a	Ligand L^b	Conversion (%)	ee (%)	Absolute configuration
1	**1**-P(O)$_2$O	**9**-P(O)$_2$N	50	72	*R*
2	**1**-P(O)$_2$O	**10**-P(O)$_2$N	100	55	*R*
3	**3**-P(O)$_2$O	**9**-P(O)$_2$N	30	68	*R*
4	**3**-P(O)$_2$O	**10**-P(O)$_2$N	40	73	*S*
5	**4**-P(O)$_2$O	**9**-P(O)$_2$N	100	35	*R*
6	**4-P(O)$_2$O**	**10-P(O)$_2$N**	**100**	**87**	***S***
7	**4**-P(O)$_2$O	**11**-P(O)$_2$N	100	63	*S*
8	**4**-P(O)$_2$O	**12**-P(O)$_2$N	100	28	*S*
9	**4**-P(O)$_2$O	**16**-P(O)$_2$N	100	54	*S*
10	**5**-P(O)$_2$O	**9**-P(O)$_2$N	100	60	*R*
11	**5**-P(O)$_2$O	**10**-P(O)$_2$N	100	22	*S*
12	**6**-P(O)$_2$O	**9**-P(O)$_2$N	100	64	*R*
13	**6**-P(O)$_2$O	**10**-P(O)$_2$N	100	21	*R*
14	**6**-P(O)$_2$O	**13**-P(O)$_2$N	100	46	*R*
15	**7**-P(O)$_2$O	**15**-P(O)$_2$N	100	31	*R*
16	**7**-P(O)$_2$O	**16**-P(O)$_2$N	100	32	*S*

[a] Standard reaction conditions for the library screening (ligand heterocombinations): the ligands (0.002 mmol L^a and 0.002 mmol L^b) were weighed and treated at room temperature, under argon, with dry DCM (1.0 mL) and $Rh(COD)_2BF_4$ (0.002 mmol, 0.8 mg). After 45 min, a solution of methyl *N*-acetamido acrylate (0.2 mmol, 28.6 mg) in dry DCM (1.0 mL) was added. The mixture was purged with H_2, and stirred for 60 h. Conversions and ee's were determined by GC equipped with a chiral capillary column (MEGADEX DACTBSβ, diacetyl-*t*-butylsilyl-β-cyclodextrin).

phosphoramidites, and the highest enantiomeric excesses (ee's) were around 52–55%.

By using combinations of two ligands, 115 different reactions were run (120 heterocombinations minus 5 combining enantiomers). Selected results are shown in Table 2, Scheme 2. By mixing two phosphoramidite ligands (data not shown), the hydrogenation product was generally obtained in moderate ee (lower than with the corresponding homocombinations), and poor conversion. The only exception was with the **11**-P(O)$_2$N/**15**-P(O)$_2$N heterocombination, which gave the reaction product in 61% ee (*S*) and 30% conversion [compare with the results using **11**-P(O)$_2$N and **15**-P(O)$_2$N: 44% ee (100% conversion) and 13% ee (30% conversion), respectively (Table 1)]. The phosphite–phosphite combinations (data not shown) gave the product quantitatively, but with poor ee's. The phosphite–phosphoramidite combinations were the most productive, retaining the phosphite high reactivity (resulting in high conversions) and often improving the enantioselectivities compared to the homocombinations (see selected examples in Table 2). The matched combination **4**-P(O)$_2$O/**10**-P(O)$_2$N (entry 6) gave the hydrogenation product quantitatively and in 87% ee, which was further improved by optimisation of the reaction conditions (solvent, ligand to rhodium ratio). Under optimised conditions (*i*-PrOH, L^a:L^b:Rh = 1.5:1.5:1, H_2 = 1 bar, 60 h) the **4**-P(O)$_2$O/**10**-P(O)$_2$N heterocombination proved to be extremely effective and enantioselective (100% yield, 94% ee).

In summary, we have synthesised a library of 16 chiral tropos ligands, 8 phosphites [P(O)$_2$O **1**–**8**] and 8 phosphoramidites [P(O)$_2$N **9**–**16**]. This ligand library allowed



Scheme 2.

the screening of 16 homocombinations and 115 heterocombinations for the rhodium catalysed asymmetric hydrogenation of methyl *N*-acetamido acrylate. Every homocombination resulted in a dynamic 'in situ' library, with up to three different species theoretically present in solution (RhL^aL^a, $RhL^aL^{a'}$, $RhL^{a'}L^{a'}$), while every heterocombination resulted in potentially 10 different species: RhL^aL^a, $RhL^aL^{a'}$, $RhL^{a'}L^{a'}$, RhL^bL^b, $RhL^bL^{b'}$, $RhL^{b'}L^{b'}$, RhL^aL^b, $RhL^aL^{b'}$, $RhL^{a'}L^b$, $RhL^{a'}L^{b'}$. Altogether, up to 508 different Rh-complexes may have been generated and screened. The screening of this large number of chiral Rh-complexes resulted in the identification of the **4**-P(O)$_2$O/**10**-P(O)$_2$N heterocombination, which proved to be extremely effective and enantioselective in the hydrogenation of methyl *N*-acetamido acrylate (100% yield, 94% ee). We are currently investigating the scope of this methodology using other prochiral olefins.

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20. Phosphites [$P(O)_2O$ **1**–**8**] were prepared by reaction of the commercially available chiral alcohol with PCl_3 (THF, room temperature), followed by addition of a mixture of the appropriate biphenol and triethylamine in THF.[21] 2,2′-Dihydroxy-3,3′,5,5′-tetra-*tert*-butylbiphenyl was synthesised by oxidation of 2,4-di-*tert*-butylphenol with potassium manganate.[22] Phosphoramidites [$P(O)_2N$ **9**–**16**] were synthesised by treatment of the appropriate chiral secondary amine with PCl_3 in the presence of triethylamine (toluene, 70 °C, 6 h), followed by a solution of biphenol in toluene at −78 °C.[23] Bis-[(*S*)-1-naphthalen-1-yl-ethyl]-amine and bis-[(*R*)-1-naphthalen-1-yl-ethyl]-amine were prepared via a reported one-pot procedure.[24] (2*S*,*S*)-2,5-Diphenylpyrrolidine and (2*R*,*R*)-2,5-diphenylpyrrolidine were prepared as reported.[25] Generally, the ligands were purified via flash-chromatography, to give the products as white foamy solids. All the ligands showed a singlet by ^{31}P NMR ($CDCl_3$): **1**-$P(O)_2O$ $\delta = 152.8$; **2**-$P(O)_2O$ $\delta = 152.8$; **3**-$P(O)_2O$ $\delta = 147.7$; **4**-$P(O)_2O$ $\delta = 151.5$; **5**-$P(O)_2O$ $\delta = 145.4$; **6**-$P(O)_2O$ $\delta = 153.4$; **7**-$P(O)_2O$ $\delta = 146.7$; **8**-$P(O)_2O$ $\delta = 147.0$; **9**-$P(O)_2N$ $\delta = 147.6$; **10**-$P(O)_2N$ $\delta = 147.6$; **11**-$P(O)_2N$ $\delta = 149.6$; **12**-$P(O)_2N$ $\delta = 149.6$; **13**-$P(O)_2N$ $\delta = 150.1$; **14**-$P(O)_2N$ $\delta = 150.1$; **15**-$P(O)_2N$ $\delta = 149.2$; **16**-$P(O)_2N$ $\delta = 149.2$. All the ligands gave consistent ^{1}H and ^{13}C NMR spectral data, which are available from the corresponding authors upon request.
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