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Improving conversion and enantioselectivity in hydrogenation by combining different monodentate phosphoramidites; a new combinatorial approach in asymmetric catalysis†

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The combination of monodentate ligands in the rhodium-catalysed enantioselective hydrogenation enables a new approach when searching for the optimal activity and enantioselectivity in catalysis.

Rhodium-catalysed asymmetric hydrogenation of prochiral olefins is continuously expanding as an important methodology in the industrial preparation of chiral building blocks. During more than three decades, the supremacy of bidentate chiral phosphines as ligands for transition metal catalysts used in asymmetric hydrogenation has been undeniable.[1] As a common view in the field, bidentate ligands were considered as a *conditio sine qua non* in order to achieve an effective enantioselective hydrogenation.[2] However, this rife idea has recently been questioned since monodentate phosphorus ligands have led to enantioselectivities and rates comparable to or better than those reached with bidentate ligands reported so far.[3]

Recently reported examples[4] show that monodentate phosphorus ligands have the advantage of being readily accessible, highly diverse, and extraordinarily inexpensive compared to various privileged bidentate ligands. Due to the coordination environment of the metal, the catalytically active species in the rhodium-catalysed asymmetric hydrogenation should have either a single bidentate or two monodentate ligands. We realised that this feature has an additional crucial advantage: when screening monodentate ligands, mixtures of ligands should give rise to the presence of a hetero-complex $Rh(L_1)(L_2)$, besides the corresponding homo-complexes $Rh(L_1)_2$ and $Rh(L_2)_2$. The mixed catalyst might well be more effective than the homo-complexes.

Although mixing chiral ligands to improve the enantioselectivity has been previously reported in asymmetric catalysis, this was only done with combinations of chiral bidentate ligands.[5] We explored this new concept for the enantioselective catalytic hydrogenation of β-dehydroamino acids. The very recent disclosure of Reetz and co-workers of a similar approach for the hydrogenation of α-dehydroamino acids,[6] prompted us to communicate our independent results for β-amino acids synthesis.

In the course of a study to find an efficient ligand for the enantioselective hydrogenation of β-dehydroamino acid derivatives,[7] we carried out a systematic optimization of the structure of MonoPhos™ (**1**, Fig. 1). Different monodentate phosphoramidites were prepared and tested in this specific asymmetric hydrogenation. We observed that monophosphoramidites with two alkyl chains on the nitrogen led to both moderate conversion and enantioselectivity when used as ligands in the Rh-catalysed hydrogenation of (*Z*)-β-(acylamino)acrylates **7** and **8** (Scheme 1). Remarkably, among those tested only ligand (*S*,*R*)-**2**, carrying a single alkyl chain on nitrogen, afforded good conversion and ee. Moreover, ligand **2** turned out to form a remarkably fast catalyst, comparable to the *state of the art* bidentate ligands.[8] Bearing these facts in mind, the traditional approach to further optimize the ee in this particular hydrogenation would be the modification of the structure of ligand **2**, by preparing analogues with both a hydrogen and different alkyl chains attached to the nitrogen (NH ligands). Ligand **2** was obtained from MonoPhos *via* amine exchange, and was easily isolated and purified by crystallization mainly due to its insolubility in most of the organic solvents.[7,8] Unfortunately, the solubility behaviour of this ligand proved to be an exception in the NH series, and other monodentate NH-phosphoramidites prepared with different alkyl chains appeared to be highly soluble. In addition, although phosphoramidites are usually stable enough to be purified by column chromatography (*e.g.*, **1**, **3**–**6**),[9] in the case of analogues of ligand **2** this is a problematic task.

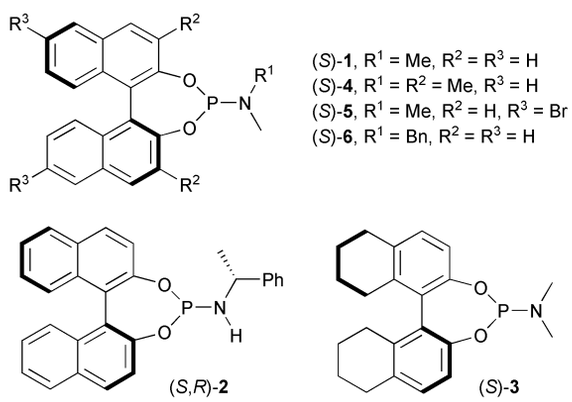
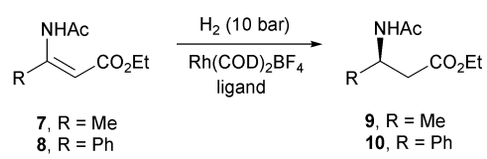


Fig. 1 Monodentate phosphoramidites.



Scheme 1 Asymmetric hydrogenation of (*Z*)-β-(acylamino)acrylates **7**–**8**.

This entanglement encouraged us to improve the ee not by modifing the ligand, but the actual catalytic species. This could be done by simply mixing the most effective ligand [(*S*,*R*)-**2**]

† Electronic supplementary information (ESI) available: Experimental details. See http://www.rsc.org/suppdata/ob/b3/b302097e/

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Table 1 Combinations of monophosphoramidites[a]

Entry	Ligand L_1	Ligand L_2	Entry	Ligand L_1	Ligand L_2
1	**1**	**1**	7	**2**	**1**
2	**3**	**3**	8	**2**	**3**
3	**4**	**4**	9	**2**	**4**
4	**5**	**5**	10	**2**	**5**
5	**6**	**6**	11	**2**	**6**
6	**2**	**2**			

[a] Reactions were performed using 1 equiv. of each ligand L_1 and L_2 with respect to Rh. See Figs. 2 and 3 for ee and conv results for each entry.

with different monophosphoramidites prepared in our laboratories. We tested this approach by carrying out parallel experiments in a single run, using a 96-vessels autoclave.[10] The hydrogenation of substrates **7** and **8** was tested using 1 mol% of $Rh(COD)_2BF_4$ as precatalyst, 10 bar of H_2 and four different solvents (i-PrOH, DCM, AcOEt and THF) with 2 mol% of ligands **1**–**6**. In a parallel experimental set-up we compared these reactions with the combination of ligand **2** (1 mol%) with one of the other ligands (**1**, **3**–**6**, 1 mol%) under the same conditions. In general, it turned out that in all reactions in which ligand **2** was present, irrespective if single ligands or mixtures of ligands were used, the ee's and conversions were higher than those obtained in the remaining experiments. Remarkably, experiments carried out in DCM as solvent showed that all the ee's obtained using only one particular ligand (entries 1–6, Table 1 and Fig. 2) were lower than those obtained from the combination of ligands (entries 7–11).[11] For example, in the asymmetric hydrogenation of substrate **7** in DCM, the ee obtained was 54% and 80% when using 2 equiv. of ligand **4** and **2**, respectively (entries 3 and 6, blue, Fig. 2). *However, the use of a mixture of those ligands (1 equiv. each), surprisingly led to 91% ee (entry 9).* Moreover, although conversions obtained with single ligands **1** and **3**–**6** were only moderate (entries 1–5, Fig. 3), combinations of those with ligand **2** (entries 7–11) afforded conversions above 88%, comparable to the conversion reached with the Rh/**2** homo-catalyst (entry 6).

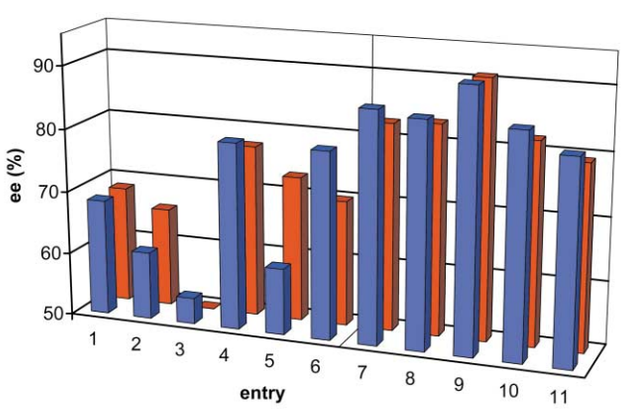

Fig. 2 Enantioselectivities obtained using single ligands (entries 1–6) or combinations with ligand **2** (entries 7–11) in the hydrogenation of **7** (blue) and **8** (red). See Table 1.

A combinatorial screening on mixtures of monodentate ligands (Table 2) can be extremely useful in asymmetric catalysis. Screening the entire matrix allows an easy comparison of homo- (diagonal) and hetero- (off-diagonal) catalysts and provides an internal duplo measurement.

In summary, this new concept based upon the combination of different monodentate ligands expands current approaches when searching for the optimal enantioselective and active catalyst.

Table 2 Combinatorial approach to the ligand combinations[a]

	L_1	L_2	L_3	. . .	L_n
L_1	ML_1L_1	ML_2L_1	ML_3L_1		
L_2	ML_1L_2	ML_2L_2	ML_3L_2		
L_3	ML_1L_3	ML_2L_3	ML_3L_3		
. . .					
L_n					ML_nL_n

[a] Out of the diagonal, the mixture of ligands can form not only the hetero- but also the homo-complexes of the metal with both ligands.

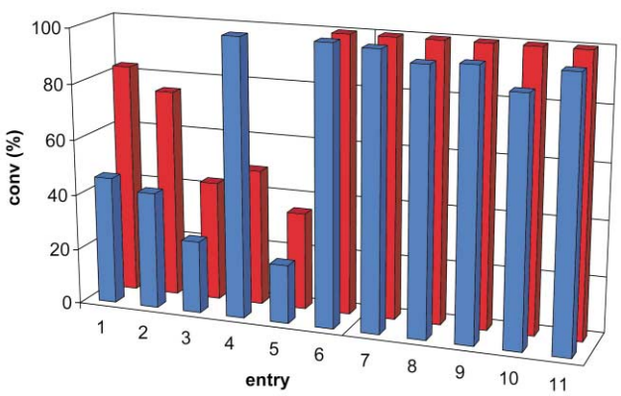

Fig. 3 Conversions obtained using single ligands (entries 1–6) or combinations with ligand **2** (entries 7–11) in the hydrogenation of **7** (blue) and **8** (red). See Table 1.

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10 Reaction mixtures were prepared under argon in an automated way by a robot using stock solutions of precatalyst, ligands and substrates. See supplementary information † for experimental details and the whole set of results from a run.
11 This effect was not noticed when using a different solvent.