



Speciality Chemicals Magazine

JANUARY 2011
Volume 31 No. 01

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Novel chiral catalysts for health and life sciences

Dr Torsten Irrgang and Dr Kathrin Kutlescha of AIKAA Chemicals introduce some novel chemocatalysts*

The manufacturing of synthetic chiral pharmaceuticals, vitamins, agrochemicals, flavours and fragrances is highly challenging, because the enantiomers are difficult to separate and very often only one of them is biologically active.

Many technologies compete for the production of enantiopure or enantioenriched compounds, such as the separation of enantiomers, chiral pool approach, biocatalysis and

chemocatalysis. The first is still the dominant technology, accounting for over half of the production of enantioenriched pharmaceuticals, but it is not very sustainable. Large amounts of solvent have to be handled and 50% of the material with the wrong absolute configuration has to be either recycled or discarded.¹

Chemocatalysis, by contrast, is superb in terms of its atom economy, large-scale production potential,

sustainability and synthetic scope. It is a key technology for the direct and efficient synthesis of chiral compounds. Introducing highly selective chemocatalysts that are simple in their structure, cost-efficient and easy to synthesise could greatly change the relative importance of the alternative technologies.

Recently, we reported on two novel structural types of efficient and highly enantioselective hydrogena-

tion catalysts for simple ketone and *N*-aryl imine reduction.^{2,3} The chiral ligands are easy to make from inexpensive starting materials and the synthesis involves a classic one-pot organic benchtop reaction. The modular nature of this multi-component procedure ensures the introduction of a broad variety of substitution patterns.

Chemocatalysts based on the phosphane-ruthenium-diamine

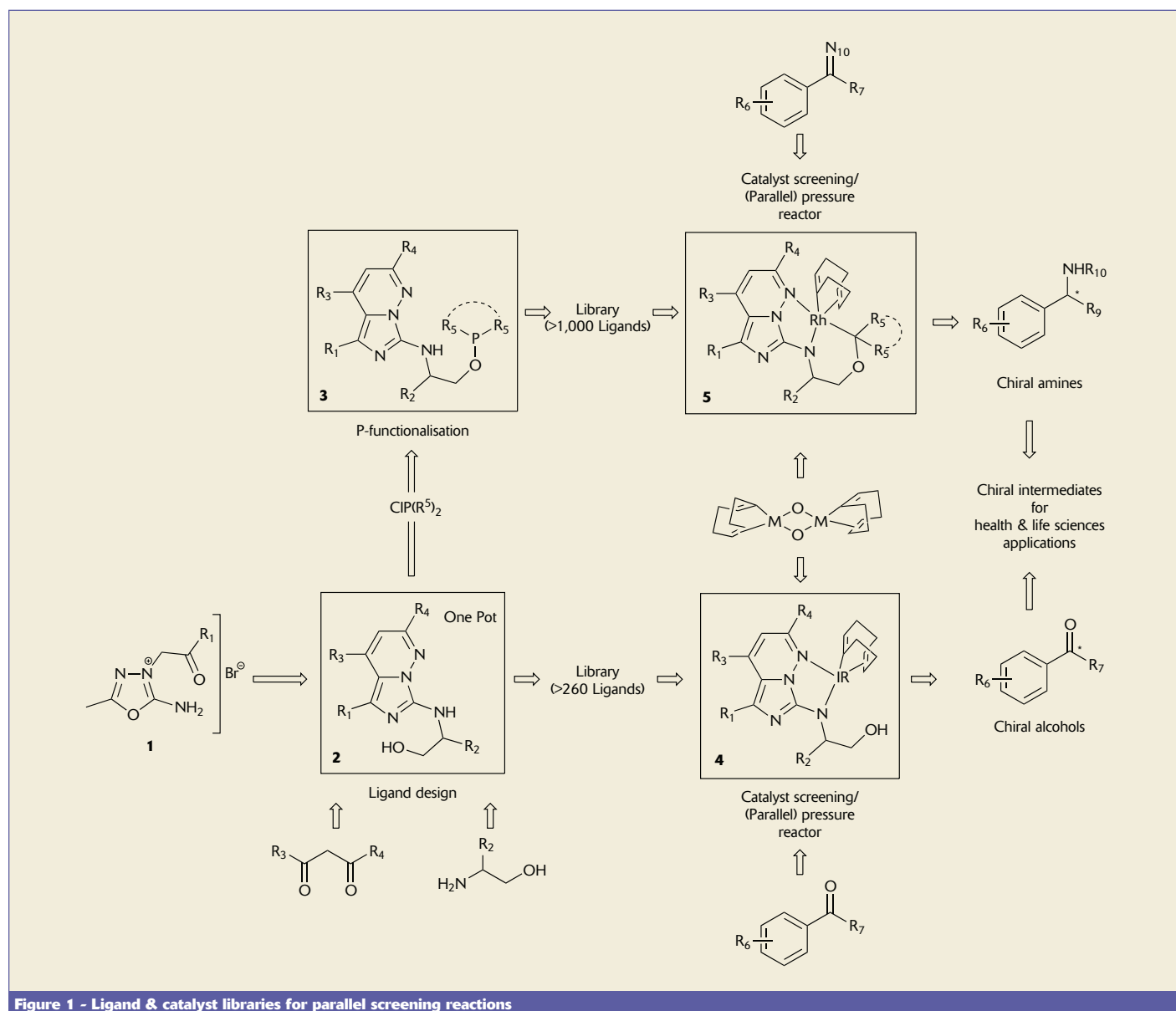


Figure 1 - Ligand & catalyst libraries for parallel screening reactions

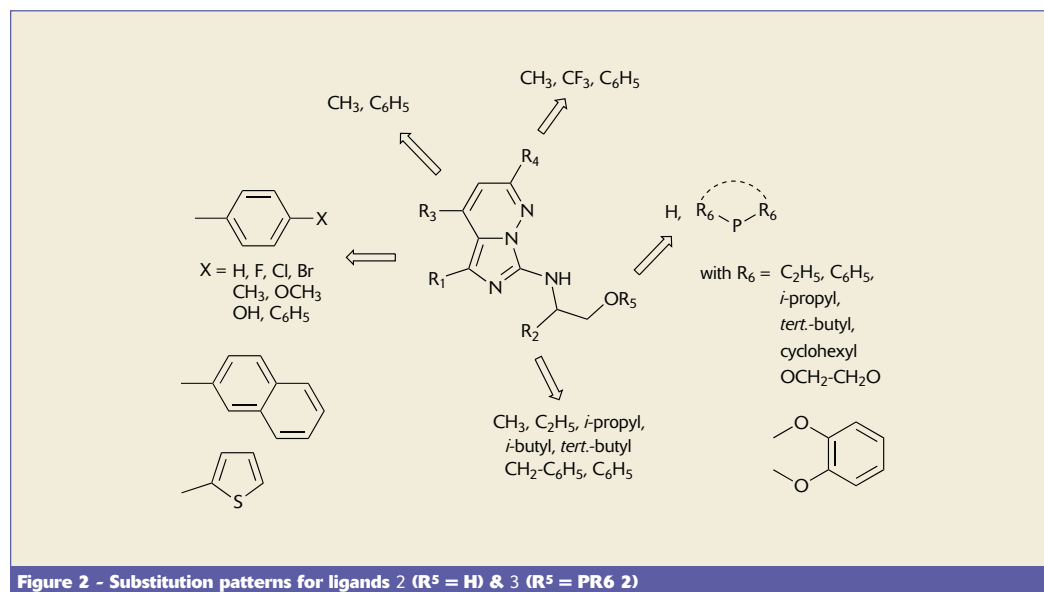


Figure 2 - Substitution patterns for ligands **2** ($R^5 = H$) & **3** ($R^5 = PR_6 2$)

complexes developed by Noyori and catalysts derived from this structural type of coordination compound are the most successful available systems for ketone hydrogenation.^{4,5} During the past decade, various enantioselective imine hydrogenation catalysts have been introduced, mostly cationic iridium complexes based on neutral P,N-ligands, for instance phosphino-oxazolines or P,N-ferrocenes.⁶

Results & discussion

The preparation of imidazo[1,5-*b*]pyridazine-substituted amido ligands that stabilise early and late transition metal complexes, can be performed via ring transformation and a subsequent cyclocondensation reaction.⁷

Starting from 2-amino-5-methyl-1,3,4-oxadiazolium halogenides (Figure 1, **1**) a variety of amino alcohol substituted imidazo[1,5-*b*]pyridazines (**2**) can be prepared in a one-pot reaction.⁸ The modular nature of this protocol means that a broad variety of substitution patterns can be introduced and a large library of more than 216 moisture and air-stable chiral (*R* and *S* configuration) **2** ligands synthesised (Figure 2).

Through the P-functionalisation of **2**, a novel amido ligand class (**3**) is accessible in good to excellent yields and high purities. Lithiation with *n*-BuLi selectively occurs at the O-atom of the hydroxyl group. Subsequently, one equivalent of dialkyl- or diaryl-chlorophosphine or ethylene chlorophosphite is added, giving rise to **3** as viscous orange products.

The ligands are available on an individual basis and can be purchased separately directly from AIKAA-Chemicals or additionally as a ligand/catalyst toolkit. This includes ligands with a variety of substituents for steric and electronic fine-tuning and a metal precursor. Thus, the pre-catalysts can easily be prepared *in situ* for **4** by mixing air- and moisture-stable reactants.

Starting from $IMOCH_3(cod)_2I$ ($M = Ir, Rh$; COD = 1,5-cyclooctadiene), the late transition metal amido complexes **4** and **5** were prepared via methanol elimination in THF at room temperature in quantitative yields (Figure 2). The metal atom is stabilised by the formation of a five-membered chelate.

Further studies

Initial hydrogenation experiments (20 bar H_2 pressure, room temperature, 24 hours, 0.05-0.1 mol% catalyst loading) without base addition revealed low activity and selectivity for all of the investigated complexes **4** and **5**. Since KOtBu can act as a ketone hydrogenation catalyst itself - if rather harsh conditions are applied - we investigated its potential as an additive.

The addition of KOtBu to 1-0.05 mol% of **4** as a pre-catalyst gave rise to complete conversion of the model substrate, which was propiophenone. The enantioselectivity increases significantly with reducing the catalyst concentration. Two conclusions were drawn from this study.

First, KOtBu is needed as an additive. Secondly, the enantioselectivity of the catalyst system seems to increase during hydrogenation catal-

ysis, since an increased ee with a lowered catalyst loading is observed. If a highly enantioselective catalyst species is formed during catalysis, the addition of ketones, which are hydrogenated in parallel and preferentially faster, should support its formation and thus improve the overall enantioselectivity.

Acetone was found to be a suitable non-prochiral ketone additive. Complexes **4** show an increased enantioselectivity if acetone is added as a co-substrate. The substituent at the asymmetric carbon atom of the amino alcohol moiety makes it possible to tune the catalyst family to provide an ee of >99%.

The substituent at the imidazole ring is rather ee-inert and might be used to fine-tune catalyst solubility or to craft the catalyst onto a support. A 2:1 acetone to propiophe-

none ratio is optimal in order to reach high enantioselectivity and to maintain a high level of activity with regards to the conversion of the prochiral ketone.

N-Aryl imines represent another interesting substrate class for the asymmetric hydrogenation. Initial hydrogenation experiments (0.1 mol% **5**, 24 hours, 40°C, 60 bar H_2 pressure) with complexes **5** ($M = Ir, Rh$) showed, that rhodium amido complexes are the most promising catalyst systems. Upon the addition of KOtBu complete conversion of the model substrate *N*-(1-phenylethylidene)aniline and 82% ee could be achieved.

Selectivity could be increased from 82% to 90% (room temperature, 20 bar H_2 pressure) by optimising the reaction conditions. The selectivity was not observed to be pressure-dependent at 5-60 bar. The substituents at the asymmetric carbon atom of the amino alcohol moiety and at the P atom allow for the fine-tuning of the catalyst towards the substrate.

Other parameters

Having optimised important reaction parameters like ligand, co-catalyst and additives, it was of interest to broaden the substrate scope and address the general applicability of catalyst systems **4** and **5** in terms of enantioselectivity. Figure 3 shows a variety of arylalkyl ketones that were hydrogenated with high and excellent enantioselectivities using **4**.

Comparable selectivity data (>99% ee) were obtained with Noyori-type catalysts for **6**, **7** and

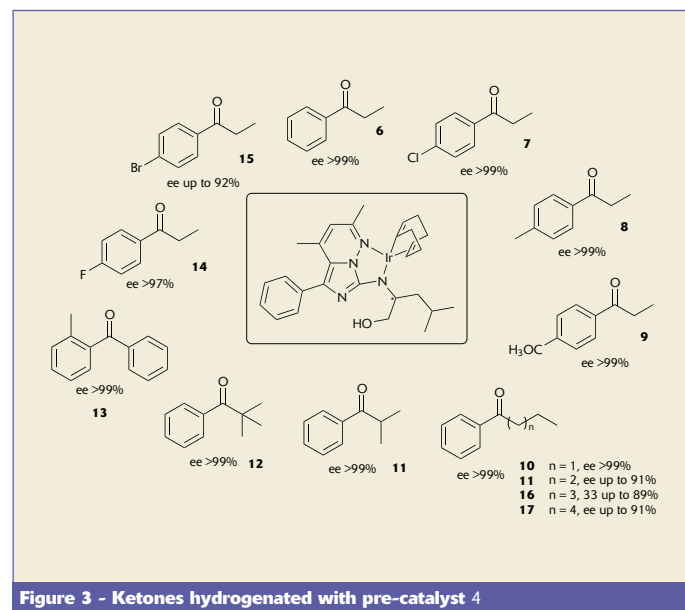
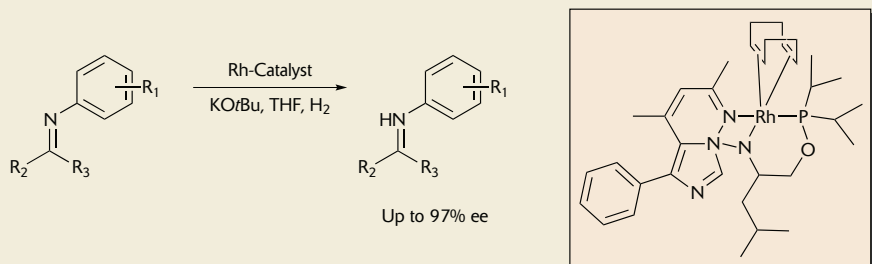


Figure 3 - Ketones hydrogenated with pre-catalyst **4**

Table 1 - Hydrogenation of *N*-aryl imines with pre-catalyst 5


Entry	R ₁	Imine R ₂	R ₂	Yield ^a (%)	ee ^b (%)
1 [#]	H	C ₆ H ₅	CH ₃	>99	90
2	H	4-CH ₃ -C ₆ H ₅	CH ₃	97	86
3	4-OCH ₃	C ₆ H ₅	CH ₃	>99	82
4	3-CH ₃	C ₆ H ₅	CH ₃	>99	89
5 ^{*#}	3,5-CH ₃	C ₆ H ₅	CH ₃	98	90
6	3-CH ₃	4-CH ₃ -C ₆ H ₅	CH ₃	>99	87
7 [#]	4-OCH ₃	4-CH ₃ -C ₆ H ₅	CH ₃	>99	75
8 [#]	4- <i>n</i> -C ₄ H ₉	4-CH ₃ -C ₆ H ₅	CH ₃	>99	83
9	H	C ₆ H ₅	C ₂ H ₅	>99	76
10 [#]	H	C ₆ H ₅	C ₅ H ₁₁	>99	74
11 [*]	H	C ₆ H ₅	<i>t</i> -C ₄ H ₉	>99	57
12 [*]	H	4-Br-C ₆ H ₅	CH ₃	35	97
13 [*]	H	3,4-OCH ₃ -C ₆ H ₅	CH ₃	74	89
14 [#]	H	2-Naphtyl	CH ₃	57	91

Notes: 0.1 mol% (*0.2 mol%) **5**, KOtBu, 48 hours (#24 hours), room temperature, 20 bar H₂; a - determined via GC; b - determined via HPLC

11. Leading literature values with such catalysts in terms of enantioselectivity reach 95% ee for **8** and **9**, 94% for **10**, 97% for **12** and 93% for **13**.^{4,10}

The resulting alcohol from **13** is an intermediate for the synthesis of orphenadrine, one of the biological active components in a variety of drugs, such as Norflex, Norgescic and Disipal. For PhanePhos-ruthenium-diamine catalysts, **6** and **11** can be hydrogenated with 98% and 71% ee respectively.¹¹

Additionally, the catalyst system based on **4** showed exceptional long-term stability. A catalyst loading of 5 ppm led to 99% ee and a conversion of 87% within 504 hours. Scale-up was investigated for the hydrogenation of **6** and **11**. Both alcohols can be synthesised with 0.05 mol% catalyst loading at 100 ml product scale, with quantitative conversion and an ee of >99%.

High enantioselectivities, similar to those in the best known literature systems, can be obtained in the asymmetric hydrogenation of various *N*-aryl imines with **5** (Table 1).¹² Due to the anionic nature of the supporting ligand, higher hydrogenation efficiency was observed

than in most of these literature systems. The catalyst loading could be reduced to 0.1-0.2 mol%, as against typically 1 mol% in the literature. The high efficiency and enantio-

selectivity could also be verified in a first preparative experiment. In this, 2.5 gm of *N*-phenyl(1-phenylethyl) amine was isolated in a 83% yield and with 89% ee.

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Conclusion

The reported amido-complexes represent novel classes of efficient and easily accessible catalysts for the asymmetric hydrogenation of simple ketones and imines with numerous advantages. The novel amido ligands **2** and **3** are very simple in their structures and easy to make from inexpensive starting materials. Due to the modular design, broad substitution patterns can be realised.

The high efficiency and good selectivity combined with the novel structural motif opens up new prospects for enantioselective hydrogenation. The results described here may initiate research in enantioselective synthesis towards structural simplicity and may help to increase the applicability of chemocatalysts in the life sciences.

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