Asymmetric Catalysis

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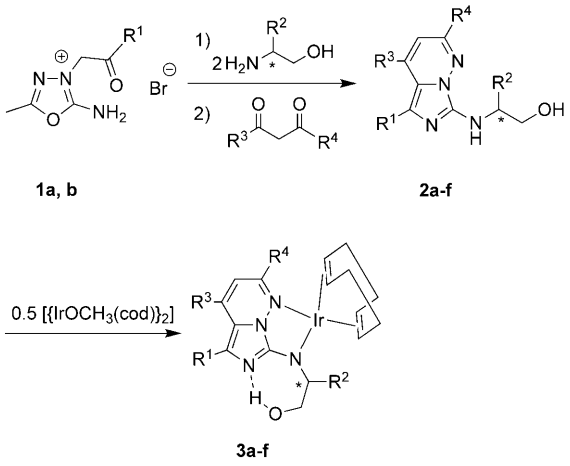
Highly Enantioselective Amido Iridium Catalysts for the Hydrogenation of Simple Ketones**

*Torsten Irrgang, Denise Friedrich, and Rhett Kempe**

In the production of chiral compounds chemocatalysis competes with other techniques such as, for example, the resolution of racemates, the "chiral pool" approach, and biocatalysis. Highly enantioselective chemocatalysts based on simple and inexpensive ligands could drastically increase the importance of chemocatalysis.[1] We report here on highly enantioselective phosphorus-free catalysts with a novel structure for the hydrogenation of simple ketones.[2] The chiral ligands can be synthesized in a one-pot reaction starting from inexpensive chemicals. The modular nature of this synthesis ensures the introduction of a broad variety of substitution patterns. The catalyst synthesis starts with air- and moisture-stable substrates. Until now, chemocatalysts based on the phosphane–ruthenium–diamine complexes developed by Noyori, catalysts related to this structural type,[3,4] and more complex chelate systems[5] have been the most successful catalysts for the asymmetric hydrogenation of ketones. In contrast, phosphorus-free (iridium) catalyst systems are drastically less efficient and/or enantioselective in this asymmetric hydrogenation.[6]

Imidazo[1,5-*b*]pyridazine-substituted amines, which can serve as amido ligands to stabilize early- and late-transition-metal complexes, can be synthesized by ring transformation and a subsequent cyclocondensation reaction.[7] Starting from 2-amino-5-methyl-1,3,4-oxadiazolium halides **1**[8] (Scheme 1) amino alcohol substituted imidazo[1,5-*b*]pyridazines **2** were prepared in a one-pot reaction in yields ranging from 50 to 60%. The iridium amido complexes **3** were prepared in quantitative yields from **2** and $[\{IrOCH_3(cod)\}_2]$[9] (cod = 1,5-cyclooctadiene) by methanol elimination in THF at room temperature (Scheme 1). The molecular structure of **3b** is shown in Figure 1.

The iridium atom is stabilized by the formation of a five-membered chelate (N1, N2, C9, N4, Ir). The Ir–N_{amido} bond [2.031(3) Å] is significantly shorter than the Ir–$N_{pyridazine}$ bond [2.149(4) Å)] indicating the localization of the negative charge of the ligand at the N_{amido} atom. The hydroxyalkyl moiety forms a hydrogen bond with N3 of the imidazole ring [d(O1H10···N3) = 1.949 Å].



Scheme 1. Synthesis of **2** and **3** (**a**: $R^1 = t$Bu, $R^2 = H$, $R^3 = R^4 = CH_3$; **b**: $R^1 = C_6H_5$, $R^2 = CH_2CH(CH_3)_2$, $R^3 = R^4 = CH_3$; **c**: $R^1 = t$Bu, $R^2 = CH_2CH(CH_3)_2$, $R^3 = R^4 = CH_3$; **d**: $R^1 = C_6H_5$, $R^2 = CH(CH_3)_2$, $R^3 = R^4 = CH_3$; **e**: $R^1 = C_6H_5$, $R^2 = CH_2CH_3$, $R^3 = R^4 = CH_3$; **f**: $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = R^4 = CH_3$).

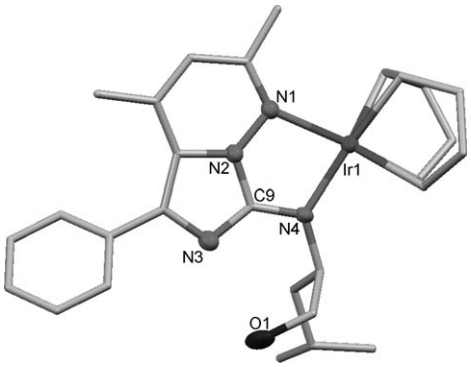


Figure 1. Molecular structure of **3b** (ORTEP plot); non-carbon atoms at the 50% probability level, H atoms not shown. Selected bond lengths [Å] and angles [°]: Ir1–N1 2.149(4), Ir1–N4 2.031(3), N1–N2 1.383(5), N2–C9 1.343(5), N4–C9 1.345(5); N1-Ir1-N4 80.6(13), C9-N4-Ir1 113.1(3), N2-N1-Ir1 106.2(2), N2-C9-N4 118.3(4), N3-C9-N4 132.3(4).

Iridium amides can undergo heterolytic H_2 cleavage to generate amino iridium hydrides,[10] which are analogues of amino ruthenium hydrides, the proposed intermediates in the hydrogenation of ketones with state-of-the-art phosphane–ruthenium–diamine ketone catalysts.[3,4,11] Additional evidence for this analogy is provided by recently developed rhodium amide catalysts.[12] Hydrogenation experiments

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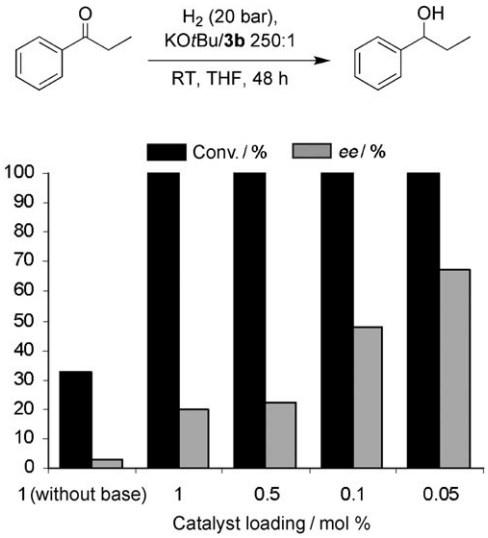

Figure 2. Hydrogenation of propiophenone with **3b** in the presence of KO*t*Bu.

Table 1: Asymmetric hydrogenation of propiophenone.

Entry	Precatalyst	Acetone/ propiophenone	Conv. [%][b]	*ee* [%][b]
1	**3a**[a]	–	>99	0
2	**3a**[a]	2:1	>99	0
3	**3b**[a]	–	>99	71
4	**3b**[a]	2:1	>99	>99
5	**3c**[a]	–	>99	37
6	**3c**[a]	2:1	>99	>99
7	**3d**[a]	–	>99	65
8	**3d**[a]	2:1	>99	97
9	**3e**[a]	–	>99	39
10	**3e**[a]	2:1	78	89
11	**3f**[a]	–	>99	31
12	**3f**[a]	2:1	51	78
13	**4b**[c]	–	0	0
14	**4b**[d]	–	93	71
15	**4b**[d]	2:1	90	99

[a] Reaction conditions see Figure 2, 0.05 mol% **3a–f**. [b] Conversion and *ee* were determined by GC. [c] 0.05 mol% **4b**, 24 h, 20 bar H_2, RT. [d] 0.05 mol% **4b**, KO*t*Bu/**4b** 250:1, 24 h, 20 bar H_2, RT.

under the conditions listed in Figure 2 revealed low activity and enantioselectivity for all investigated complexes **3a–f**. The addition of KO*t*Bu leads to quantitative conversion with **3b** as a precatalyst with catalyst loadings of 1, 0.5, 0.1, and 0.05 mol% (Figure 2). KO*t*Bu itself is a catalyst for the hydrogenation of ketones under drastic conditions,[13] and its potassium cations accelerate the reaction rate of phosphane–ruthenium–diamine complexes.[14a]

With a decrease of the catalyst loading the enantioselectivity increases significantly. Without KO*t*Bu and with 1 mol% of **3b** a conversion of only 33% and an enantioselectivity of only 3% *ee* is observed. Two conclusions can be drawn from these observations. Firstly, KO*t*Bu is needed as an additive. Secondly, the enantioselectivity of the catalyst system seems to increase during the hydrogenation. Two phenomena could explain the increase of the enantioselectivity with progressing catalysis: autocatalysis as well as the formation of a yet more enantioselective species during the hydrogenation. The addition of (*S*)-(−)- or (*R*)-(+)-1-phenylpropan-1-ol (autocatalysis) did not significantly increase the enantioselectivity. If a more enantioselective catalyst species is formed during catalysis, the addition of a (non-prochiral) ketone, which is hydrogenated in parallel, could increase the enantioselectivity. The increase in enantioselectivity could result from the fact that the more enantioselective catalyst species is already formed before a significant amount of the unwanted enantiomer is produced. Acetone turned out to be a useful additive. The catalytic performance (hydrogenation of propiophenone) of **3a–f** with KO*t*Bu and acetone was examined (Table 1). The addition of acetone as a cosubstrate leads to an increase in enantioselectivity for all chiral catalyst systems (entries 3–12). The enantioselectivity of the catalyst can be optimized by adjusting the steric bulk of the substituent at the asymmetric carbon atom of the amino alcohol such that selectivities of >99% *ee* can be obtained (entries 4 and 6) under the given conditions. The substituent at the imidazole ring is little effect on the *ee* and might be used to fine-tune the solubility of the catalyst. An acetone/propiophenone ratio of 2:1 is optimal to reach high enantioselectivity and to maintain a high level of activity in the conversion of the prochiral ketone.

The reaction of **3** with KO*t*Bu is accompanied by a clear color change from dark turquoise to red and gives rise to the bimetallic complex **4**. The molecular structure of **4b** is shown in Figure 3; that of **4a** is given in the Supporting Information.

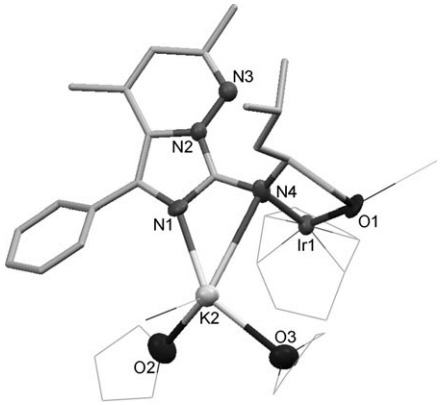

Figure 3. Molecular structure of **4b**. (ORTEP plot); non-carbon atoms at the 50% probability level, H atoms not shown. Selected bond lengths [Å] and angles [°]: N1–K2 2.748(10), N4–Ir1 2.007(10), N4–K2 3.313(9), O1–Ir1 1.992(9), N1-K2-N4 45.4(3).

The hydroxy moiety is deprotonated by KO*t*Bu, and an iridium amido–alkoxo complex is formed. The chiral carbon atoms of the amino alcohol moiety of **2b–f** are in close proximity to the iridium atom through the formation of five-membered C-O-Ir-N-C chelates which may explain the increased enantioselectivity of the heterobimetallic complexes. The potassium atom in **4b** has strained η^2-*N*,*N* coordination. The binding of the potassium atom to the amido N atom may enhance the heterolytic H_2 cleavage.[11b,14]

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If **4b** is used as a catalyst without added base, the reaction mixture turns blue, which indicates formation of **3b** and hydrogenation becomes very slow (Table 1, entry 13). The products of the catalysis compete with the OH moiety of the ligand in terms of metalation. To shift the equilibrium towards **4b**, an excess of KO*t*Bu is essential under catalysis conditions (Table 1, entry 14 and 15).

Having optimized important reaction parameters like the ligand, co-catalyst, and ketone additive, we set out to broaden the substrate scope. The aryl ketones shown in Figure 4 were hydrogenated with excellent enantioselectivities (> 99 % *ee*) using the catalyst system based on **3b**.

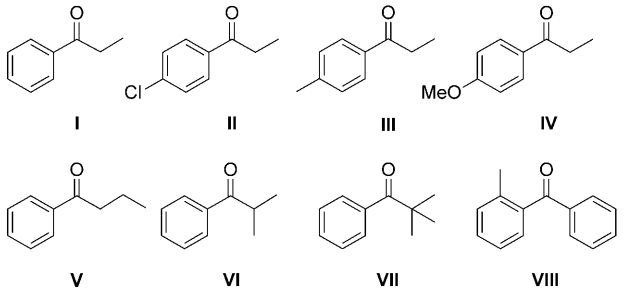

Figure 4. Ketones hydrogenated with > 99 % *ee* by using **3b** as a precatalyst. The following conversions were observed: **I** and **III**–**VII** > 99 %, **II** of 97 %, and for the significantly slower reaction of **VIII** 70 %.

To obtain these high enantioselectivities an excess of KO*t*Bu relative to the iridium complex is necessary. The yield of the resulting alcohols correlates with the ketone conversion. The following yields were obtained for the correspond alcohols prepared from these ketones: **I** 96 %, **III** 98 %, **IV** 95 %, **V** 98 %, and **VI** 97 %. Comparable selectivity (>99 % *ee*) was obtained with Noyori-type catalysts for ketones **I**, **II**, and **VI**.[3a] The best reported enantioselectivies with such catalysts reach 95 % *ee* for **III** and **IV**,[3a] 94 % *ee* for **V**,[3a] 97 % *ee* for **VII**,[4p] and 93 % *ee* for **VIII**.[15] The alcohol resulting from **VIII** is an intermediate in the synthesis of orphenadrine, one of the biologically active components in a variety of drugs such as Norflex, Norgesic, and Disipal. With PhanePhos–ruthenium–diamine catalysts (PhanePhos = 4,12-bis(diphenylphosphanyl)[2.2]paracyclophane) **I** and **VI** could be hydrogenated with 98 and 71 % *ee*, respectively.[16]

In addition the catalyst system based on **3b** proved to be exceptionally stable over time. A catalyst loading of 5 ppm led to 99 % *ee* and a conversion of 87 % after a reaction time of 504 h. We examined the hydrogenation of ketones **I** and **VI** on a larger scale. Both alcohols can be synthesized with 0.05 mol % catalyst on a reaction scale of 100 mL with quantitative conversion and > 99 % *ee*.

In conclusion, we have introduced a modular phosphorus-free ligand system. These ligands stabilize Ir–K catalyst complexes, which hydrogenate simple ketones with excellent enantioselectivities. We showed that highly enantioselective, but structurally simpl catalysts can be obtained easily from inexpensive starting materials. The new lead structure presented here should stimulate the search for simple and inexpensive catalyst structures for enantioselective syntheses and thus a higher acceptance of chemocatalysts in life-science applications.

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