Asymmetric Hydrogenation

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High Enantioselectivity Is Induced by a Single Monodentate Phosphoramidite Ligand in Iridium-Catalyzed Asymmetric Hydrogenation**

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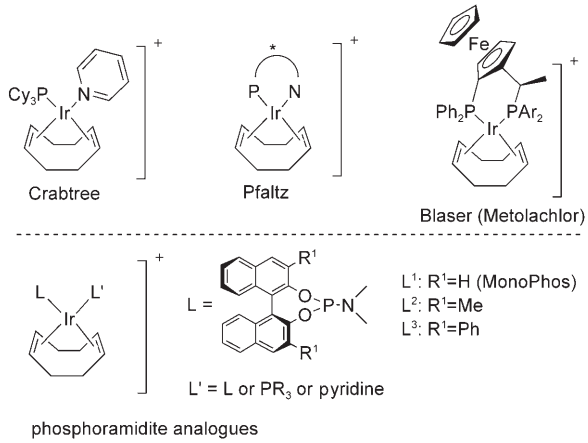
Bidentate chiral ligands were the rule in metal-catalyzed asymmetric hydrogenation for more than 30 years[1] as chelation was believed to be necessary to impart the necessary rigidity to the metal complex for an efficient transfer of chirality. Recently, however, a few groups have demonstrated that monodentate ligands can also induce high enantioselectivity[2] as long as two of these ligands are present in the active species. Herein, we describe the first example of a highly asymmetric hydrogenation that is induced by a metal catalyst containing only one monodentate ligand.[3]

Iridium is an important metal in hydrogenation. The Crabtree catalyst,[4] its enantioselective version, developed by Pfaltz, based on chiral P,N ligands,[5] or the celebrated Metolachlor process catalyst[6] are prime examples of Ir-based hydrogenation catalysts (Scheme 1). We were interested in investigating whether iridium complexes of chiral monodentate phosphoramidites could also act as efficient enantioselective hydrogenation catalysts. Although such Ir complexes have already been reported,[7] which has led to the discovery of new cyclometalated species that are active in allylic substitution,[8] there are no reports of their use in enantioselective hydrogenation.

Our initial studies were aimed at the preparation of cationic iridium complexes that are analogues of the Crabtree catalyst containing a phosphoramidite ligand L, and either the same phosphoramidite, a phosphine, or pyridine as the secondary ligand L′ (Scheme 1). Based on literature precedents,[9] two equivalents of Monophos were treated with [{Ir(cod)Cl}$_2$] to immediately give [Ir(cod)(L)Cl][7b] which, upon chloride abstraction in the presence of another equivalent of L, should form a cationic complex of the type [Ir(cod)LL′]$^+$. Although we screened several phosphoramidites in combination with different ancillary ligands and counteranions, we did not obtain an efficient hydrogenation catalyst. The breakthrough came with the observation that an active but also enantioselective catalyst is obtained with bulky phosphoramidites based on Binol with substituents in the 3,3′ positions without abstraction of the chloride ligand, that is, from the non-cationic catalyst precursor [Ir(cod)(L)Cl] containing only one phosphoramidite ligand per metal.[10]



Scheme 1. Iridium catalysts.

The drastic effect of the substitution in the 3,3′ positions of the diol backbone of the ligand can be visualized by comparing the hydrogen uptake curves obtained during the hydrogenation of methyl (*Z*)-2-acetamidocinnamate (Figure 1). Figure 1 clearly shows that increasing the bulkiness of the chiral backbone in the 3,3′ positions leads to a substantial increase not only in activity but also in enantioselectivity (average TOFs of 6, 24, 50, and 150 h^{-1} and *ee* values of 28, 67, 93, and 98% for R^1 = H, Me, Ph, and R^2 = *t*Bu, respectively; see also Scheme 1). For practical reasons, namely that the diol precursor is commercially available, the bulkiest ligand with the *t*Bu substituents is based on biphenol while the other ligands are based on binaphthol.[12] Increasing the bulkiness of the phosphoramidite by changing its amino moiety does not, however, produce the same effect, and the catalytic performance of the complex remained poor when the dimethylamino group was substituted by a bis(α-methylbenzyl)amino group with unsubstituted binaphthol as backbone. This indirectly reinforces our assumption about the major role played by substitution in the 3,3′ positions of the

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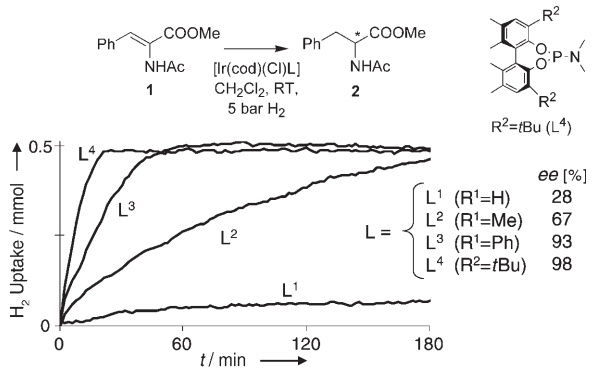


Figure 1. Hydrogen consumption during the hydrogenation of methyl (*Z*)-2-acetamidocinnamate with various Ir/phosphoramidite catalysts (Ir/L/substrate = 0.01/0.01/0.5 mmol).[11]

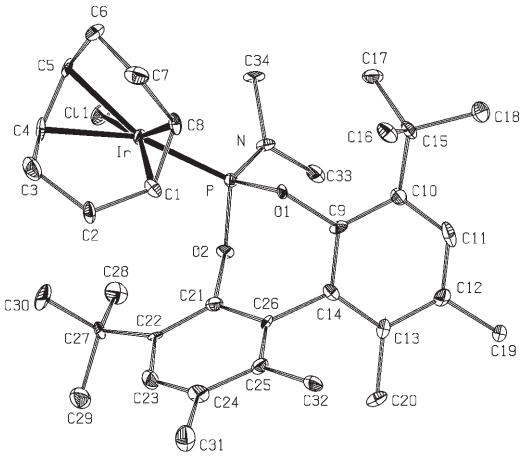


Figure 2. ORTEP representation of the structure of [Ir(cod)(L^4)Cl]; selected bond lengths [Å] with estimated standard deviations: Ir-Cl 2.362(2), Ir-P 2.265(3), Ir-C1 2.126(9), Ir-C4 2.224(10), Ir-C5 2.232(10), Ir-C8 2.143(9), C1-C8 1.435(16), C4-C5 1.397(17).

ligand diol backbone. A similar effect has also been reported by Ojima for rhodium-catalyzed hydroformylation reactions.[12]

In order to confirm that the catalyst precursor contains only one phosphoramidite ligand per metal ion, we undertook a full characterization of the complex by NMR spectroscopy, X-ray diffraction, and elemental analysis. The addition of two equivalents of L^4 to $[Ir(cod)Cl]_2$ (Ir/L = 1/1) led to the complete disappearance of the ^{31}P NMR signal of the free ligand L^4 at $\delta = 141.1$ ppm and the appearance of a single peak at $\delta = 107.8$ ppm (bound L^4). If more L^4 is added, no change is observed except for the appearance of the free-ligand peak. The behavior of L^1 is different. Thus, if more than two equivalents of L^1 per $[Ir(cod)Cl]_2$ is used, a new Ir complex exhibiting two sets of doublet ($\delta = 94.5$ and 88.6 ppm, $J = 38.6$ Hz) is observed in addition to a singlet at $\delta = 117.6$ ppm for [Ir(cod)(L^1)Cl]. This pattern is consistent with an iridium complex containing two nonequivalent L^1 moieties.

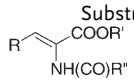
Crystals of the complex formed upon reaction of $[Ir(cod)Cl]_2$ with L^4 were obtained from a dichloromethane/heptane solution and studied by X-ray diffraction. The crystal structure of this complex is presented in Figure 2.[13]

Although the catalyst precursor was fully characterized as a complex containing a single phosphoramidite ligand, the ligand-to-iridium ratio may be more than one in the active species responsible for the hydrogenation. However, several facts seem to prove that this is not the case:

1. *Bulky ligands are necessary for activity and enantioselectivity*: As we have seen previously, the less bulky L^1, which is more suitable for formation of an $[Ir(L^1)_2]^+$ complex, does not lead to an active catalyst although it is electronically equivalent to L^4. This seems to demonstrate that a bulky ligand is necessary to stabilize an [IrL] species. It might also help to prevent dimerization, which is a common cause of deactivation of iridium hydrogenation catalysts.[4b]
2. *No acceleration is observed in the presence of additional ligand*: If one additional equivalent of ligand L^4 is added to isolated [Ir(cod)(Cl)L^4] prior to the hydrogenation, the hydrogenation reaction proceeds slightly slower. The opposite would be observed if the active species were of the type $[IrL_n]$ ($n > 1$) as more of this species would be present in solution.
3. *The absence of a nonlinear effect*:[14] The *ee* value of **2** varies linearly with that of the ligand L^4.[15] For phosphoramidites[16a] and phosphonites,[16b] a positive nonlinear effect has been observed in the case of Rh, where it is accepted that the active species contains two ligand molecules per metal ion.
4. *The absence of a ligand mixture effect:* One of the advantages of monodentate ligands in an ML_2 complex is the possibility of using mixtures of ligands L_a and L_b to form new catalysts of the type ML_aL_b.[17] The addition of one equivalent of (*R*)-L^1 to [Ir(cod)((*S*)-L^4)Cl] prior to the hydrogenation does not decrease the *ee* value of **2**. Although this chiral poisoning experiment does not constitute a definite proof, it shows that the active hydrogenation species containing L^4 does not accommodate an extra phosphoramidite ligand L^1 to form the cation $[Ir((S)\text{-}L^4)((R)\text{-}L^1)]^+$.

We briefly investigated the scope of the catalyst with various amino acid precursors (Table 1). The catalyst exhibits high activity and enantioselectivity with both electron-poor and electron-rich substituted methyl (*Z*)-2-acetamidocinnamates (Table 1, entries 2 and 3). A high *ee* value is also obtained upon hydrogenation of the acid, although the catalysis becomes rather slow (Table 1, entry 4). With smaller substrates such as methyl 2-acetamidoacrylate (Table 1, entry 5), the *ee* value drops to 50%. A further drop is observed when the *N*-acetyl group is replaced by an *N*-formyl group (Table 1, entry 6).[18] However, increasing the bulk of the alkyl residue of the substrate again leads to a high *ee* value (Table 1, entry 7). A standard enamide (*N*-(1-phenylvinyl)-acetamide) was also tested under the same conditions. It gave full conversion but only a low *ee* value (10%). These results are quite informative. First of all, they show that a single-ligand catalyst is more efficient with relatively bulky substrates. Such substrates might form a more rigid assembly with

Table 1: Conversion and *ee* values obtained with [Ir(cod)(L^4)Cl] in the hydrogenation of various dehydroamino acids.[a]

Entry	Substrate			Conv. [%]	TOF [h^{-1}][b]	*ee* [%]
						
	R	R′	R″			
1[c]	Ph	Me	Me	100	150	98
2	*p*-MeOC$_6$H$_4$	Me	Me	100	25	98
3	*p*-ClC$_6$H$_4$	Me	Me	100	25	98
4	Ph	H	Me	50	9	98
5	H	Me	Me	100	273	50
6	H	Me	H	89	30	39
7[d]	*i*Pr	Me	H	89	1	88

[a] Ir/L/substrate = 0.01/0.01/0.5 mmol, CH_2Cl_2, room temperature, 5 bar H_2. [b] Average TOF estimated from H_2 consumption curve. [c] The hydrogenation of this substrate was also performed at 25 bar H_2, which led to an increase in rate but no change in *ee*. [d] Substrate/catalyst ratio of 25:1.

the catalyst because of steric congestion, thus allowing an efficient transfer of chirality. Secondly, although we cannot rule out η^6 coordination in the case of the phenylalanine precursor[19] as an explanation for the *ee* value obtained with this substrate, this is not a prerequisite, as observed in entry 7 of Table 1.

Although the true nature of the active species in homogeneous catalysis is often difficult to ascertain unambiguously, our observations point towards an iridium complex with a single monodentate ligand as the active species. We believe this is a unique example of high enantioselectivity induced by a catalyst that has been pared down to the bare essentials. It is conceivable, though, that secondary interactions between iridium and the monodentate ligand are induced either due to an η^2 interaction[20] or C–H insertion[8,21] upon hydrogenation of cod, which would transform our monodentate ligand into a bidentate ligand. We are currently investigating the structure of the catalyst during hydrogenation by NMR spectroscopy and mass spectrometry.

Experimental Section

General procedures: All reactions were performed under dry nitrogen using standard Schlenk techniques or in a glove box. Anhydrous solvents dried over molecular sieves (Fluka) were used systematically. [{Ir(cod)Cl}$_2$] and Biphen were purchased from Strem. The hydrogenation substrates were synthesized following published procedures.

Preparation of [Ir(cod)(L^4)Cl]: [{Ir(cod)Cl}$_2$] (65 mg, 0.096 mmol) was placed in a 10-mL Schlenk flask and the entire apparatus was evacuated and back-filled with N_2 three times to establish an inert atmosphere. Dry, degassed dichloromethane (1 mL) and (*S*)-L^4 (82 mg, 0.192 mmol) were added and the reaction mixture was stirred at room temperature for 10 min. X-ray quality crystals were obtained upon layering with *n*-heptane. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.22$ (s, 1H), 7.09 (s, 1H), 5.40–5.29 (m, 1H), 5.24–5.13 (m, 1H), 3.57–3.47 (m, 1H), 2.83–2.74 (m, 1H), 2.61 (br, 3H), 2.58 (br, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.80 (s, 3H), 1.71 (s, 3H), 1.65 (s, 9H), 1.37 ppm (s, 9H); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 107.8$ ppm; elemental analysis calcd (%) for $C_{34}H_{50}ClIrNO_2P$: C 53.49, H 6.60, N 1.83; found: C 53.4, H 6.8, N 1.8.

Hydrogenation experiments: The hydrogenation experiments with monitoring of the H_2 consumption were performed in an Endeavor reactor. The Endeavor is an autoclave that contains eight reactors equipped with glass reaction vessels. Substrate (0.5 mmol), [{Ir(cod)Cl}$_2$] (0.01 mmol), and ligand (0.02 mmol) were weighed into these reaction vessels. The vessels were placed in the reactors and CH_2Cl_2 (5 mL) was added. The reactors were purged for 30 min with N_2 before applying a hydrogen atmosphere of 5 bar. The pressure was kept constant during the reaction and the hydrogen uptake was monitored. After completion of the reaction, the reactors were opened and samples were taken for *ee* determination by GC.

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