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Isolation of an σ-Alkyl Iridium Hydride Complex, Formed in the (Semi)hydrogenation of an β-Enamido Ketone

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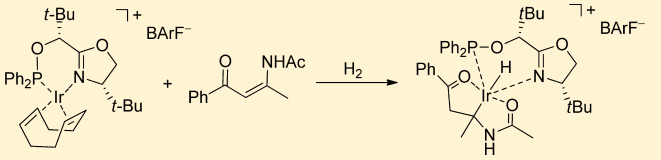
Supporting Information

ABSTRACT: σ-Alkyl iridium hydride complexes are generally postulated as intermediates in iridium-catalyzed hydrogenation. Fast reductive elimination results in the formation of the hydrogenation product. With an β-enamido ketone as unsaturated substrate, such an intermediate could be trapped because the semihydrogenated product coordinates trifold to the iridium, generating a stable 18e⁻ complex, which does not eliminate.



During the last decades, asymmetric catalytic hydrogenations became a powerful tool for the stereoselective synthesis of a wide range of chiral compounds.[1] Rh-[2] and Ru-catalyzed[3] hydrogenations in the presence of various types of chiral ligands, in particular, have found widespread applications.[4,5] Good results are generally obtained with functionalized substrates such as enamides and dehydro amino acid derivatives, while unfunctionalized alkenes are critical substrates for these catalysts.[6] In this case, Ir-catalyzed hydrogenations were found to be superior.[7−19] In addition, they give also good results with aryl-substituted α,β-unsaturated ketones.[20−23] While hydrogenations of amino-functionalized alkenes with Ru- and Rh-catalysts are well developed, only a few reports describe Ir-catalyzed hydrogenations of α-[24,25] and β-didehydroamino acid esters,[26,27] enamides,[28,29] and enamines.[30−33] Especially with the last class of substrates, good results are obtained with bidentate PHOX-ligands, e.g., ThrePHOX (**A**) (Figure 1).[34] Very recently, we showed that similar

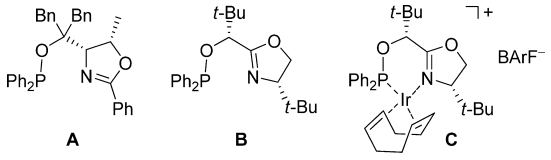


Figure 1. Chiral ligands used in Ir-catalyzed hydrogenations.

phosphinitoxazolines (**B**) are especially suited for the Ir-catalyzed hydrogenation of α,β-unsaturated ketones.[35] Excellent ee's were obtained with acyclic (**1**) and cyclic aryl-substituted ketones (**2**) (Figure 2) if the Ir(COD) complex **C** (Figure 1) was used as catalyst.

To determine the scope and limitations of this catalyst system, we investigated the hydrogenation of a wide range of other unsaturated substrates. No reaction was observed in the hydrogenation of phenyl-substituted acrylates, allyl alcohols, enol ethers, and phosphates or α-hydroxy ketones. Only a slow conversion was observed in case of a α,β-didehydrophenylalanine derivative **3**, giving rise to the chiral amino acid with

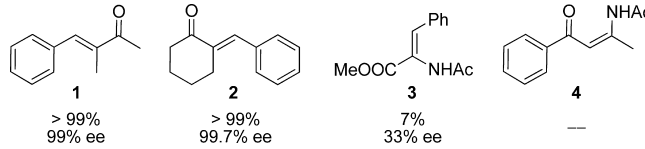


Figure 2. Hydrogenation of unsaturated substrates with complex **C**.

moderate ee. In the case of β-amido-substituted α,β-unsaturated ketones such as **4**, no hydrogenation product could be found (Figure 2). The high chemoselectivity for the α,β-unsaturated ketones should allow their selective hydrogenation in complex molecules, as long as the other functionalities present do not interfere in the hydrogenation process.

Therefore, we investigated not only hydrogenations of single compounds but also mixtures thereof. If mixtures of different α,β-unsaturated ketones were subjected to hydrogenation a clean conversion was observed, and the ee′ values were comparable to the single compound hydrogenation, as expected. The reactions were monitored by GC, and the different reaction rates of the different components provided important information about the influence of the substitution pattern on the reactivity. An interesting observation was made in hydrogenations of mixtures of different classes of compounds. In particualr, if β-amido ketone **4** was present in the reaction mixture, the hydrogenation of the α,β-unsaturated ketones was suppressed completely. This was an astonishing effect since substrates such as **4** are suitable substrates, e.g., for asymmetric Rh-catalyzed hydrogenations.[36−38] But in our case, they not only failed to get hydrogenated but also seemed to inhibit the hydrogenation of other compounds. Therefore, we assumed that the β-amido ketone interacts with the catalyst, resulting in its deactivation.

This caused us to investigate the hydrogenation of α,β-unsaturated ketone **5** in the presence of various amounts of **4** in

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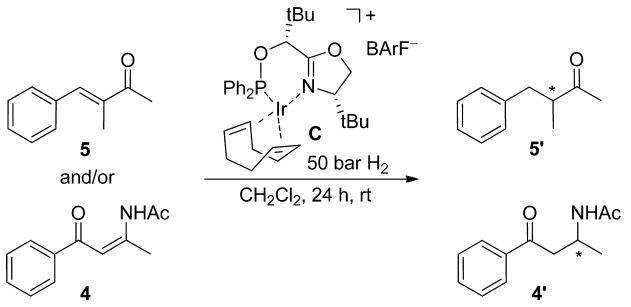
detail (Table 1).[39] While a clean conversion was observed in the hydrogenation of pure **5** (entry 1), already the addition of only 1% of **4** resulted in a dramatic drop in the yield, although the ee′ value was (more or less) unchanged (entry 2). Not surprising, no hydrogenation was observed if the amidoketone was added in stoichiometric amounts (entry 3). Obviously, a 1:1 ratio of amido ketone and catalyst results in a significant deactivation of the catalyst. We assumed that **4** can coordinate to the catalyst without being hydrogenated (no hydrogenated **4**′ could be determined by GC). In a second set of experiments, we added different amounts of catalyst to a solution of pure **4** and determined the consumption of **4** by GC (entries 4 to 7). A linear correlation was observed, indicating that probably a 1:1 complex (**6**) is formed.

Table 1. Catalytic Hydrogenations Using Iridium Complex C



entry	**5** (equiv)	**4** (equiv)	**C** (mol %)	conversion (%)	ee (%)
1	1		1	91 (**5**)	99.1
2	1	0.01	1	9 (**5**)	99.4
3	1	1	1	<1 (**5**)	
4		1	1	1 (**4**)	
5		1	10	11 (**4**)	
6		1	25	27 (**4**)	
7		1	50	50 (**4**)	

To identify this new compound **6**, we carried out the hydrogenation under 1 atm of H_2 with a 1:1 ratio of catalyst and substrate. After 2 h, the color of the solution changed from orange to yellow. Although some starting material was left, a definite new compound **6** could be determined by TLC. This compound could be isolated by flash chromatography and was analyzed by LCMS and NMR. The molpeak found correlated to a complex of **4**′ and the ligand/Ir complex without COD, which was also not found in the NMR spectra. In addition, the signals of the *t*-Bu groups were significantly shifted compared to **C**. Some signals were comparable to those expected for **4**′ but showed different coupling patterns. In addition, the proton at the stereogenic center was missing. The two diastereotopic H's at the adjacent CH_2 group gave two doublets without a coupling to an α-H, clearly indicating that one H-atom had been transferred to the substrate, at the negatively charged position of the enamide, but not the second one. In addition, no coupling was observed at the CH_3 group on the stereogenic center, and therefore, we postulated an Ir-σ-alkyl hydrido complex **6** was formed (Figure 3).

To confirm this proposal, we investigated also the ^{31}P NMR spectra. The signal for the phosphinite group (doublet) was shifted from 106.49 ppm (**C**) to 98.90 ppm (**6**), showing a coupling of 19.3 Hz. This value is typical for P−H couplings in hydrido complexes[40−42] and also provides information on the relative orientation of the hydride and the phosphinite in the complex. Coupling constants of around 20 Hz are typical for H-atom *cis* to P, while *trans* oriented H-atoms give couplings of

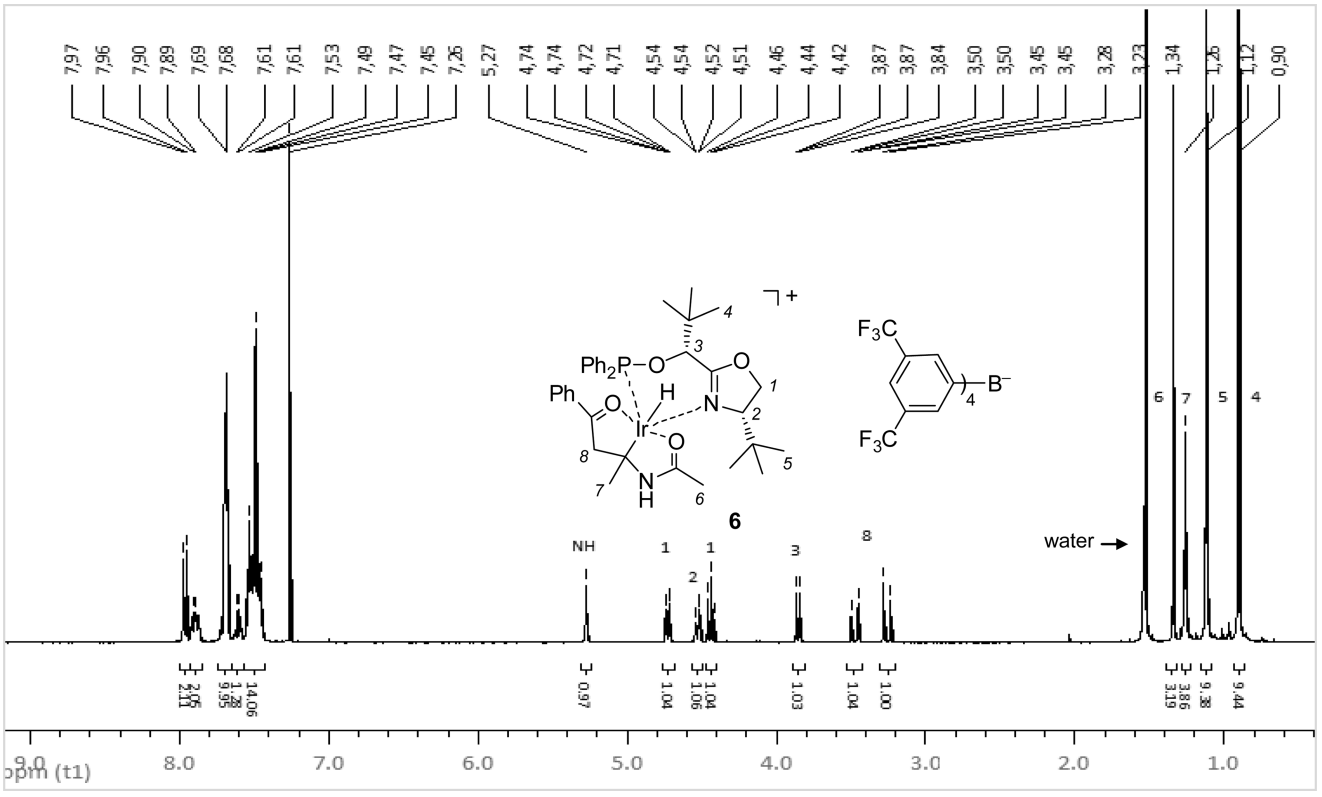


Figure 3. ^1H NMR spectrum of postulated iridium complex **6**.

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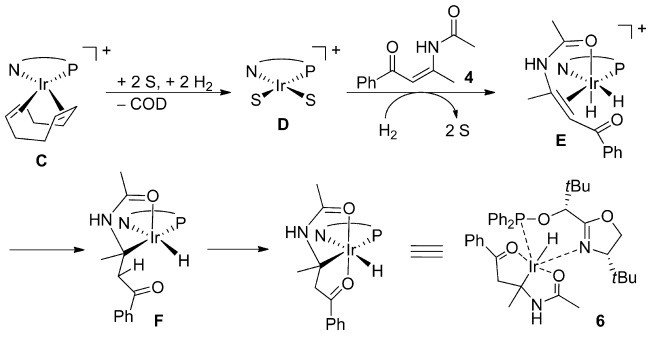
150−280 Hz. In the ^{1}H NMR spectrum the signal for the hydride in the postulated complex should be expected in the negative ppm-area. In this area the ^{31}P spectra are not H-decoupled anymore under standard conditions. This would explain the doublet observed for the P-signal. Therefore, in a second NMR experiment we suppressed the P−H couplings over the whole ppm range, and indeed, no coupling was observed and the P-signal appeared as a singlet. In the ^{1}H NMR spectrum the signal for the hydride was found at −23.3 ppm (J = 23 Hz). Also a strong downfield shift was observed for the two carbonyl groups of the amido ketone fragment (ketone: 199.3 to 216.2 ppm, amide: 169.4 to 177.4 ppm), as a result of the coordination toward the central iridium atom.

The formation of **6** can be explained by a mechanism generally discussed for catalytic hydrogenations (Scheme 1).

Scheme 1. Mechanism Proposed for the Formation of Iridium Complex 6



Probably in the first step, the COD-ligand is removed reductively providing a coordinatively unsaturated Ir^{I} complex **D**. Oxidative addition of H_2 and coordination of the substrate provides an intermediate **E**, which then undergoes insertion of the enamide into one of the Ir−H bonds. In general, such σ-alkyl transition-metal complexes **F** are postulated as intermediates in catalytic cycles of hydrogenations but could never be trapped because the last step, the reductive elimination of the hydrogenation product, is very fast. In our case, the alkene insertion generates a free rotatable σ-bond allowing the keto group also to coordinate to the Ir. The resulting 18e^{-} complex **6** is too stable to undergo reductive elimination.

CONCLUSION

In conclusion we show that σ-alkyl iridium hydrido complexes, generally postulated as intermediates in catalytic hydrogenations, can be trapped if additional coordination of functional groups in the substrate allows the generation of stable 18e^{-} complexes. In this case, the last step of the catalytic cycle, the reductive elimination, can be suppressed. Further mechanistic investigations are in progress.

EXPERIMENTAL SECTION

General Remarks. All air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of nitrogen. Solvents were dried and distilled before use using standard procedures. Melting points were uncorrected. ^{1}H, ^{13}C, and ^{31}P as well as H,H-COSY and HSQC spectra were recorded on a 400 or 500 MHz NMR spectrometer. Chemical shifts are reported in ppm with respect to TMS, and $CHCl_3$ was used as the internal standard (85% H_3PO_4 for ^{31}P). Spin−spin coupling constants J are given in hertz. Enantiomeric excess was determined by GC equipped with a CP-Chirasil-Dex capillary column (25 m × 0.25 mm). Optical rotations were determined at 20 °C at 589 nm. Mass spectra (quadrupole) were recorded using the CI technique. Hydrogenations were performed in an autoclave (300 mL). The α,β-unsaturated ketone **5**[20] and enamide **4**[38] were prepared via standard literature methods. Racemic references could be obtained by hydrogenation with Pd/C. The chiral iridium complex **C** was synthesized according to our previously reported method.[35]

Iridium-Catalyzed Hydrogenations. General Procedure. To a solution of the corresponding substrate/substrates together with the internal standard tetradecane in dry dichloromethane in a test tube was added catalyst **C**. A sample was taken and subjected to GC analysis. The tube was transferred into the autoclave. It was purged three times with nitrogen and three times with hydrogen before it was pressurized to 50 bar. The mixture was stirred at this pressure. After 24 h, the pressure was released and the tube was purged five times with nitrogen. The reaction tube was removed and the solution filtered over Celite and subjected to GC-analysis to determine conversion and selectivity. GC separation conditions T_0 [3 min] = 90 °C, 1 (°C/min) to T = 200 °C [20 min], injector 250 °C, detector 275 °C.

Synthesis of Hydrido Complex 6. In a 25 mL round-bottom flask complex **C** (78.1 mg, 50.0 μmol) and **4** (10.2 mg, 50.0 μmol) were dissolved in dichloromethane (6 mL). The mixture was stirred at 1 atm of H_2 for 2 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (SiO_2, dichloromethane) giving rise to **6** (72.4 mg, 43.7 μmol, 87%) as a yellow solid (mp 61 °C). Unfortunately, all attempts to get suitable crystals for Xray structure analysis by crystallization failed: $[\alpha]^{20}_{D}$ = −23.9 (c = 1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ −23.3 (d, $J_{H,P}$ = 23.0 Hz, 1H, Ir-H), 0.91 (s, 9H, C(CH_3)$_3$), 1.12 (s, 9H, C(CH_3)$_3$), 1.26 (s, 3H, NCCH_3), 1.34 (s, 3H, COCH_3), 3.26 (d, J = 18.7 Hz, 1H, IrCCH_2), 3.48 (d, J = 18.7 Hz, 1H, IrCCH_2), 3.86 (d, $J_{H,P}$ = 9.5 Hz, 1H, OCH), 4.44 (dd, J = 9.3, 2.1 Hz, 1H, OCH_2), 4.53 (dd, J = 3.0, 2.1 Hz, 1H, NCH), 4.73 (dd, J = 9.3, 3.0 Hz, 1H, OCH_2), 5.27 (bs, 1H, NH), 7.46−7.55 (m, ArH), 7.61 (t, J = 6.9 Hz, 1H, ArH), 7.69−7.72 (m, 9H, ArH), 7.90 (dd, J = 7.9, 6.9 Hz, 2H, ArH), 7.97 (d, J = 7.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 18.5 (q, COCH_3), 26.1 (3q, C(CH_3)$_3$), 26.8 (3q, C(CH_3)$_3$), 34.6 (s, C(CH_3)$_3$), 35.7 (d, $J_{C,P}$ = 7.1 Hz, C(CH_3)$_3$), 36.3 (q, IrCCH3), 38.3 (s, IrC), 63.4 (t, COCH2), 72.4 (t, OCH_2), 73.5 (d, NCH), 78.3 (d, $^{2}J_{4,P}$ = 5.5 Hz, OCH), 117.4 (4d, ArC), 124.5 (8q, $J_{C,F}$ = 272.6 Hz, CF_3), 128.1 (2d, $J_{C,P}$ = 10.9 Hz, ArC), 128.5 (2d, $^{3}J_{C,P}$ = 11.2 Hz, ArC), 129.0 (8q, $^{2}J_{C,F}$ = 2.6 Hz, ArC), 129.2 (2d, ArC), 130.2 (2d, ArC), 130.5 (s, ArC), 130.8 (2d, ArC), 130.9 (2d, ArC), 131.4 (s, ArC), 132.8 (d, ArC), 132.9 (d, ArC), 133.4 (d, ArC), 134.8 (8d, ArC), 136.9 (s, ArC), 161.7 (4q, $J_{C,B}$ = 49.9 Hz, ArC), 172.7 (s, CON), 177.4 (s, NCO), 216.2 (s, ArCO); ^{31}P NMR (202.5 MHz, $CDCl_3$) δ = 99.6 (d, $^{2}J_{P,H}$ = 21.5 Hz); HRMS (CI) m/z calcd for $C_{36}H_{48}IrN_2O_4P$ [M − BAr_F + H]$^{+}$ 796.2981, found 796.2979.

ASSOCIATED CONTENT

Supporting Information

LCMS and copies of NMR spectra of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Prof. G. Wenz on the occasion of his 60th birthday

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