The Use of a Planar Chiral Ligand to Effect C−H Activation with Asymmetric Induction at an Iridium Center. Dramatically Different C−H Activation Stereoselectivities for Benzene and Cyclohexane

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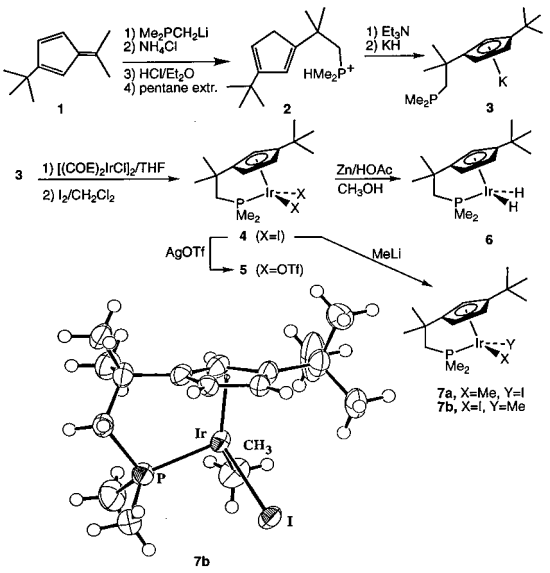
We wish to report the design and synthesis of a chelating planar prochiral ligand, its attachment to an Ir center, and the use of the resulting planar chiral[1] complex to activate the C−H bond of cyclohexane[2−4] with very high diastereoselectivity. We also find that the stereoselectivities associated with activation of C−H bonds in cyclohexane and benzene are substantially different.[5]

As our target we focused on general substituted cyclopentadienyl (Cp) structure **3** (represented as a potassium cyclopentadienide salt in Scheme 1), which contains two different substituents on the Cp ligand. One is a substituted C_2 chain connected to a dimethylphosphino group, giving a chelating ligand that can potentially confer rigidity on a derived metal complex.[6] As the second substituent we chose a *tert*-butyl group, whose bulky character should assist in controlling the stereochemistry of reactions taking place at the proximal metal center. For convenience, in the following discussion we abbreviate the ligand as "t-$^{Bu}Cp^{P}$."

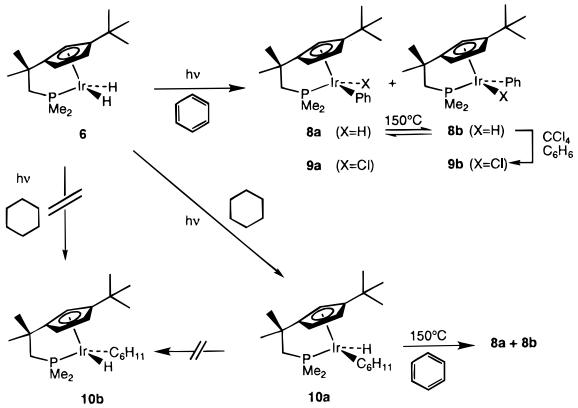
The key steps in the synthesis of the potassium salt of this ligand, as well as iridium complexes derived from it, are outlined in Scheme 1. Experimental details are provided as Supporting Information. The potassium salt **3**, prepared via compounds **1** and **2**, was converted to the diiodide complex $^{t-Bu}Cp^{P}IrI_2$ (**4**) in 78% yield. An X-ray study of **4** confirmed its structure; details are provided as Supporting Information.

The asymmetric iridium dihydride species **6** is easily synthesized (90−95% yield) by treatment of **5** with excess zinc and acetic acid in methanol (Scheme 1) after the method of Heinekey and co-workers.[7] As expected, the Ir-bound hydrogen atoms are diastereotopic, resonating in the ^{1}H NMR spectrum at δ −15.66 (dd, J_{H-P} = 24.3 Hz, J_{H-H} = 7.3 Hz) and −15.86 (dd, J_{H-P} = 24.3 Hz, J_{H-H} = 7.3 Hz). The IR spectrum shows a strong broad absorbance at 2100 cm^{-1}. An X-ray structure determination

Scheme 1



Scheme 2



(details provided as Supporting Information) has been carried out on **6**. The Ir-bound H's could not be located, but the structural study confirmed that the ligand−Ir system is intact.

Attachment of two different σ-bound ligands to the metal center in [$^{t-Bu}Cp^{P}$]M complexes leads to the formation of diastereomers. This was realized experimentally in the synthesis of air-stable $^{t-Bu}Cp^{P}Ir(Me)I$ (**7a**,**b**) by treatment of $^{t-Bu}Cp^{P}IrI_2$ (**4**) with excess MeLi. The two diastereomers were formed in a 1:1 ratio and separated by flash chromatography on SiO_2. The assignment of stereochemistry to **7a**,**b** was made by ^{1}H NOESY (Nuclear Overhauser Effect SpectroscopY) and an X-ray crystallographic study (ORTEP diagram in Scheme 1) which confirmed the assignment of the (*RR*),(*SS*) configuration to **7b**. The chelate arm is twisted which results in rotation of the cyclopentadienyl ring so that the *tert*-butyl group avoids eclipsing interaction with the Ir-bound CH_3 and I groups.

Irradiation (500 W Hanovia lamp; Pyrex filter) of a dilute C_6H_6 solution of $^{t-Bu}Cp^{P}IrH_2$ (**6**) at 10 °C resulted in darkening of the solution and formation of two new compounds identified as the diastereomeric aryl hydrides **8a** and **8b** (Scheme 2). After 5 h of irradiation two-thirds of the starting material **6** was converted to the phenyl hydrides. Integration of the hydride resonances in the ^{1}H NMR spectrum shows a 1:1 ratio of **8a**/**8b**. On a modest preparative scale, the phenyl hydrides could be separated from unreacted starting material **6** by low-temperature, air-free filtration of the mixture through a prechilled pad of SiO_2 with use of 25%

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Et_2O/pentane cooled to −40 °C. This procedure provided **8a**,**b** in a 10:7 ratio in 35% yield. The relative stereochemistry of diastereomers **8a**,**b** was assigned (as with **7a** and **7b)** on the basis of a 2D-NOESY spectrum of a 10:7 mixture of the two isomers. We further characterized the **8a**,**b** diastereomeric pair by converting them to the chlorides $^{t-Bu}Cp^{P}Ir(Cl)Ph$ (**9a**,**b**) by treatment with CCl_4 in C_6H_6. The air-stable complexes **9a** and **9b** were separated by column chromatography and isolated in 51% combined yield. The complex **9a** (39% yield) was fully characterized and identified as the (*RR*),(*SS*) isomer by a 2D-NOESY spectrum. Complex **9b** (12% yield) was identified by ^{1}H NMR and EI-MS.

Cyclohexane also undergoes photolytic C−H activation with dihydride **6**, but the stereochemistry of this reaction contrasts dramatically with that observed in the benzene reaction. Irradiation of dihydride **1** in C_6H_{12} at 15 °C results in the formation of only one product, the cyclohexyliridium hydride (*RR*),(*SS*)-$^{t-Bu}Cp^{P}Ir(H)Cy$ (**10a**, Scheme 2). The opposite diastereomer **10b** is not detected (5% detection limits). Complex **10a** was subjected to air-free, low-temperature chromatography (−80 °C, repeated twice) and isolated in 11% yield. We could not obtain this material completely pure, but we were able to characterize it spectroscopically, including high-resolution mass spectrometry of the molecular ion. As with the phenyl- and methyliridium complexes described above, the stereochemical relationships between the substituents on the cyclopentadienyl ligand and at the iridium center were established by using 2D NMR experiments.

When a C_6H_{12} solution of $^{t-Bu}Cp^{P}Ir(H)Cy$ (**10a**) was heated at 150 °C for 72 h, no change in the $^{31}P\{^1H\}$ NMR spectrum (i.e., no formation of **10b**) was observed. However, upon heating a C_6H_6 solution of $^{t-Bu}Cp^{P}Ir(H)Cy$ (**10a**) at 150 °C for 120 h, conversion to **8a** and **8b** was observed by $^{31}P\{^1H\}$ NMR spectroscopy (Scheme 2). The equilibrium constant for the interconversion of **8a** and **8b** was determined at 150 °C by $^{31}P\{^1H\}$ NMR spectrometry; this gave $K_{eq} = 0.29 \pm 0.03$ at 423 K. This value corresponds to a difference in free energy between **8a** and **8b** of $\Delta G_{423} = 1.1 \pm 0.1$ kcal/mol.

In an attempt to determine whether the interconversion of **8a** and **8b** is an intramolecular process, a 10:7 mixture of **8a** and **8b** was thermolyzed in C_6D_6 at 150 °C. After 6 h of heating, significant interconversion (10:3.5 ratio) of the diastereomers had occurred; however, very little deuterium (<3%) had been incorporated into **8a** and **8b**. After a total of 48 h of heating, some deuterium incorporation into the hydride position of **8b** was evident in the $^{31}P\{^1H\}$ NMR spectrum by the appearance of a small 1:1:1 triplet resonance that appeared slightly downfield from the phosphorus resonance of the parent compound **8b**. Integration of the *ortho*-proton resonances in the ^{1}H NMR spectrum of **8a** and **8b**, relative to one of the cyclopentadienyl resonances, indicated that little deuterium had been incorporated into the phenyl rings. This indicates, in agreement with earlier work in achiral Rh systems,[8] that the diastereomeric phenyl hydrides interconvert with η^2-benzene complexes substantially more rapidly than benzene is displaced from the metal center.

On the basis of the above results, we believe that the diastereomeric ratios observed in these photolytic reactions reflect the kinetic selectivities for the C−H bond activation reaction. This belief is based upon the fact that the equilibrium ratio of the phenyliridium hydrides **8a** and **8b** ($K_{eq} = 0.29 \pm 0.03$ at 150 °C) is reached only upon extended thermolysis even at this elevated temperature. Similarly, thermolysis of **10a** in C_6H_6 does not result in significant conversion to **8a** and **8b** until the temperature reaches 150 °C. Previously studied systems[4,9] indicate that interconversion of similar alkyl- and aryliridium hydride species occurs very slowly at temperatures below 130 °C. In the cyclohexyl case, both kinetics and thermodynamics appear to favor the essentially exclusive formation of one diastereomer.

Preliminary molecular modeling studies[10] indicate that the difference in kinetic selectivity for activation of the two substrates, cyclohexane and benzene, appears to be due to the greater steric demand of the cyclohexane ring during activation of the C−H bond. When one examines the transition state that would be required to activate a C−H bond of cyclohexane in the orientation required to form diastereomer **10b**, it is immediately apparent that there is a large unfavorable interaction between the cyclohexane molecule and the *tert*-butyl group of the cyclopentadienyl ligand. The contrasting negligible kinetic selectivity and small thermodynamic selectivity (3.5:1) observed in the benzene case can be explained by an attack on the C−H bond by the Ir center in the plane of the benzene ring, since an above-the-plane approach would appear to generate much more steric repulsion. If this interpretation of the data is correct, it would indicate that, even if an η^2 -benzene complex is formed as the initial intermediate,[8] in the subsequent C−H bond activation step the Ir lies in the nodal plane of the π-system of the benzene ring.[11]

Future experiments will be directed toward examining the stereoselectivity of C−H activation of prochiral alkane substrates, as well as studies aimed at preparing enantioenriched analogues of the molecules described here.

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Supporting Information Available: Details of the synthetic procedures for compounds **2**−**10** and details of the crystal structure determinations (including ORTEP diagrams, tables of fractional atomic coordinates, and crystal data) of compounds **4**, **6**, and **7b**, and spectroscopic and analytical data for **5** and **7**−**10** (19 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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