HYDROXYL-DIRECTED OLEFIN HYDROGENATION WITH IRIDIUM CATALYSTS.
THE DOCUMENTATION OF CATALYST : SUBSTRATE STOICHIOMETRY AS A
VARIABLE IN REACTION DIASTEREOSELECTION.

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Abstract: The present investigation documents the fact that hydroxyl-directed hydrogenation of cyclic and acyclic olefinic alcohols with the cationic iridium catalyst, Ir(COD)py(PCy3)PF6, exhibits reaction diastereoselectivity which is dependent upon catalyst-substrate stoichiometry.

Chemical reactions capable of being "directed" by resident substrate functionality have proven to be exceedingly valuable in stereoselective synthesis. The development of hydroxyl-directed hydrogenation catalysts has provided an important addition to this small but important class of reactions.1,2 Recently, we disclosed our results of a comparative study between cationic rhodium and iridium catalysts in the diastereoselective hydrogenation of both cyclic and acyclic hydroxy olefins (cf. Scheme).2

\[ \text{Scheme} \]

1. R+x
2. Me
3. RyuxN
4. Me
5. Me
6. X
7. Me
8. X

\[ \text{Equation (1)} \]

\[ \text{Equation (2)} \]
In conjunction with this study we found that while both \( \text{Rh}(\text{NBD})\text{DIPHOS}-4\text{BF}_4 \) (1) and \( \text{Ir}(\text{COD})\text{py}(\text{PCy}_3)\text{PF}_6 \) (2) \(^4\) performed remarkably well in the stereocontrolled hydrogenation of cyclic olefinic alcohols, the cationic rhodium catalyst 1 proved to be clearly superior when acyclic allylic alcohols were examined. The purpose of this Letter is to disclose additional studies which were initiated to gain a deeper understanding of the origin of the differing stereoselectivities observed with these two catalysts. Further investigation of iridium catalyst 2 in the hydrogenation of allylic alcohols 3 and 4 (Scheme) led to the unanticipated discovery that a decrease in the catalyst:substrate ratio resulted in an increase in reaction diastereoselection! This trend is quite evident in the hydrogenation of 3 \((R = \text{Me})\) with catalyst 2. At 20 mol% of iridium catalyst 2 the reduction of 3 \((R = \text{Me})\) afforded a ratio of 57:43 while at 2.5 mol% of catalyst the reaction diastereoselection improved to 85:15 (Table I).

**Table I. Stereoselective Hydrogenation of Allylic Alcohols 3 and 4 Catalyzed by Iridium Complexes 2 and 7 and Rhodium Complex 1 (Scheme).**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>20 mol%</th>
<th>2.5 mol%</th>
<th>17.5 mol%</th>
<th>17.5 mol%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3, (R = \text{Me})</td>
<td>57:43</td>
<td>85:15</td>
<td>85:15</td>
<td>93:7</td>
</tr>
<tr>
<td>3, (R = \text{Ph})</td>
<td>56:44</td>
<td>79:21</td>
<td>84:16</td>
<td>93:7</td>
</tr>
<tr>
<td>3, (R = \text{i-Pr})</td>
<td>46:54</td>
<td>52:48</td>
<td>84:16</td>
<td>94:6</td>
</tr>
<tr>
<td>4, (R = \text{Me})</td>
<td>57:43</td>
<td>27:73</td>
<td>27:73</td>
<td>9:91</td>
</tr>
<tr>
<td>4, (R = \text{Ph})</td>
<td>58:42</td>
<td>52:48</td>
<td>16:84</td>
<td>6:94</td>
</tr>
<tr>
<td>4, (R = \text{i-Pr})</td>
<td>55:45</td>
<td>50:50</td>
<td>26:74</td>
<td>8:92</td>
</tr>
</tbody>
</table>

\(\text{a}\) All product ratios determined by gas chromatography. \(\text{b}\) Carried out in anhydrous \(\text{CH}_2\text{Cl}_2\) at 15 psi \(\text{H}_2\) according to the general procedure described in Ref. 1b. \(\text{c}\) Carried out in anhydrous \(\text{CH}_2\text{Cl}_2\) at 640 psi \(\text{H}_2\) according to the general procedure described in Ref. 2. \(\text{d}\) Ref. 2 (640 psi \(\text{H}_2\)). \(\text{e}\) See Footnote 5. \(\text{f}\) Less than 10% conversion after 10 h at 15 psi hydrogen pressure.

Inspection of the data on the stereoselective reductions of all six allylic alcohols 3 and 4 \((R = \text{Me, Ph, i-C}_3\text{H}_7)\) reveals that this catalyst stoichiometry effect on reaction diastereoselection exhibits significant substrate dependence. In addition, in all but one case \((4, \text{R} = \text{Ph})\) the observed stereoselectivity was found to be independent of hydrogen pressure \((15 - 1000 \text{ psi})\). Consequently, competing catalyst-promoted olefin isomerization \((3 \approx 4)\) which might conceal the intrinsic directivity from a given hydroxy olefin is not a major side reaction responsible for the low levels of asymmetric induction observed with the iridium catalyst 2. We suspect that the above observations which document the stoichiometry-dependent reduction diastereoselectivity with the Crabtree catalyst 2 may be relatively general. For example, the reductions of both 3-methyl-2-cyclohexen-1-ol and 4-methyl-3-cyclohexen-1-ol with 2 are significantly more diastereoselective at lower catalyst concentrations (Table II).
We therefore conclude that the excellent levels of chirality transfer observed by Stork and Kahne in the directed hydrogenation of a range of cyclic hydroxy olefins with 20 mol % of the iridium catalyst 2 should constitute a minimum level of asymmetric induction for those substrates examined.\textsuperscript{1b} The nature of this inverse relationship between catalyst concentration and reaction diastereoselection is quite intriguing. Crabtree has noted that Ir(py)PCy\textsubscript{3} is deactivated via the formation of a trinuclear bridged hydride which is inactive as a hydrogenation catalyst.\textsuperscript{6} Based upon the above data we now entertain the possibility that more than one hydrogenation catalyst may be involved in reductions with 2 at high catalyst concentrations.\textsuperscript{7} For example, it is conceivable that a catalytically active polynuclear iridium species may be present which is not constrained to the same hydroxyl directivity effects as the mononuclear complex 2.

**Table II.** Hydroxyl-Directed Olefin Hydrogenation of Cyclic Substrates with the Iridium Catalyst Ir(COD)py(PCy\textsubscript{3})PF\textsubscript{6} (2).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product\textsuperscript{b}</th>
<th>Mol % \textsuperscript{2}</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ir(COD)py(PCy\textsubscript{3})PF\textsubscript{6}</td>
<td>Trans : Cis</td>
</tr>
<tr>
<td><img src="image1" alt="OH" /></td>
<td><img src="image2" alt="OH" /></td>
<td>20.0</td>
<td>50:1</td>
</tr>
<tr>
<td><img src="image3" alt="OH" /></td>
<td><img src="image4" alt="OH" /></td>
<td>2.5</td>
<td>150:1</td>
</tr>
</tbody>
</table>

\textsuperscript{2} Carried out in anhydrous CH\textsubscript{2}Cl\textsubscript{2} according to the general procedure provided in Ref. 1b. \textsuperscript{b} All product ratios determined by capillary gas chromatography. \textsuperscript{c} Data obtained from Ref. 1b.

From data illustrated in Table I it is quite evident that the cationic rhodium catalyst 1 is significantly more stereoselective than the Crabtree iridium catalyst 2 in the hydrogenation of allylic alcohols 3 and 4. Due to the differing ligands on the rhodium and iridium catalysts 1 and 2, a direct comparison of the two metals is tenuous at best. Accordingly, the iridium complex, [Ir(COD)DIPHOS-4]\textsubscript{4}BF\textsubscript{4} (7) was prepared\textsuperscript{8} and directly compared with the rhodium analog 1 in the hydrogenation of both acyclic and cyclic allylic alcohols. In the stereoselective reductions of allylic alcohols 3 and 4, Ir(DIPHOS-4)+ proved to be superior to the Crabtree catalyst Ir(py)PCy\textsubscript{3} but still less stereoselective than the rhodium analog Rh(DIPHOS-4)+ (Table I).\textsuperscript{9} On the other hand, the hydrogenation of 3-methyl-2-cyclohexen-1-ol to 3-methylcyclohexan-1-ol proved to be less selective with Ir(DIPHOS-4)+ (trans : cis = 20:1) than with Ir(py)PCy\textsubscript{3}+ (trans : cis = 50 - 150:1).
This apparent dichotomy between the observed diastereoselection of iridium catalysts 2 and 7 with cyclic and acyclic allylic alcohols underscores the lack of current understanding of the intimate details of these reactions. The results presented herein clearly demonstrate that cationic iridium complexes 2 and 7, even under optimal reaction conditions, fail to match the levels of asymmetric induction achieved by rhodium (I) catalyst 1 for acyclic allylic alcohols. Studies in these laboratories dealing with synthetic applications of this hydrogenation methodology are being explored at the present time and will be reported in due course.

Acknowledgments. This research has been supported by the National Science Foundation (CHE-8342576) and the National Institutes of Health (GM 32278-01).

References and Notes.

    (c) Crabtree, R. H.; Davis, M. W. Organometallics 1983, 2, 681.


(3) NBD = norbornadiene, DIPHOS-4 = 1,4-bis(diphenylphosphinobutane. NBD = norbornadiene, DIPHOS-4 = 1,4-bis(diphenylphosphinobutane. The detailed procedure for the preparation of 2 is provided in the supplementary material of Ref. 2. The complex, [Rh(COD)DIPHOS-4]BF4, has also been reported: Brown, J. M.; Chaloner, P. A.; Kent, A. G.; Murrer, B. A.; Nicholson, P. N.; Parker, D.; Sidebottom, P. J. J. Organomet. Chem. 1981, 216, 263.


COD = 1,5-cyclooctadiene, Cy = cyclohexyl, py = pyridine.

(5) Hydrogenation of 3 and 4 (R = Ph) were extremely slow at 15 psi hydrogen with 2.5 mol % 2. Increasing the hydrogen pressure (1000 psi) afforded similar results:3 (R = Ph), 5:6 = 75:25; 4 (R = Ph), 5:6 = 89:11.


(7) It should be noted that decreasing the concentration of 2 by solvent dilution had no effect on the reaction diastereoselection. Furthermore, decreasing the catalyst:substrate ratio below 2% had little additional effect on the reaction diastereoselection. For example, the hydrogenation of 3 (R = Me) with 1.3 mol % 2 afforded a ratio of 5:6 of 87:13. In addition, decreasing the catalyst:substrate ratio of rhodium catalyst 1 had little effect on the reaction diastereoselection.

(8) Prepared in direct analogy to the general procedure described in Ref. 2 for rhodium catalyst 1.

(9) Hydrogenation of 3 and 4 (R = Me) with 7 at 15 psi hydrogen was extremely slow and moderately selective:3 (R = Me), 5:6 = 61:39; 4 (R = Me), 5:6 = 35:63. However, isomerization was not a competing side reaction as in the case of Rh(I) analog 1.

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