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

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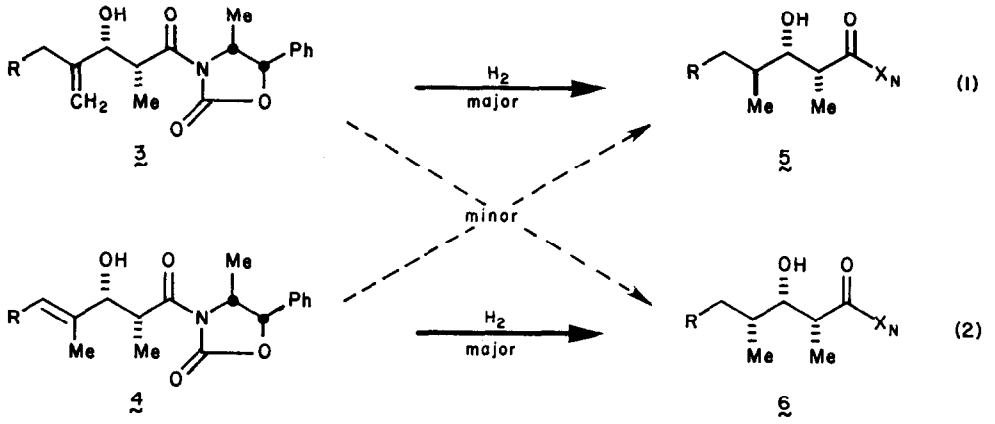
Abstract: The present investigation documents the fact that hydroxyl-directed hydrogenation of cyclic and acyclic olefinic alcohols with the cationic iridium catalyst, Ir(COD)py(PCy_3)PF_6, exhibits reaction diastereoselectivity which is dependent upon catalyst-substrate stoichiometry.

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 (c.f. Scheme).[2]

SCHEME



In conjunction with this study we found that while both $(Rh(NBD)DIPHOS\text{-}4)BF_4$ (**1**)[3] and $Ir(COD)py(PCy_3)PF_6$ (**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 = Me) with catalyst **2**. At 20 mol % of iridium catalyst **2** the reduction of **3** (R = Me) afforded a ratio of **5:6** 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).

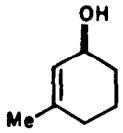
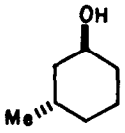
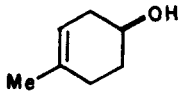
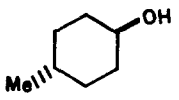
Substrate	Ratio, **5** : **6** [a,b] $Ir(COD)py(PCy_3)PF_6$ (**2**)		Ratio, **5** : **6** [c] $(Ir(COD)DIPHOS\text{-}4)BF_4$ (**7**)	Ratio, **5** : **6** [d] $(Rh(NBD)DIPHOS\text{-}4)BF_4$ (**1**)
	20 mol%	2.5 mol% [e]	17.5 mol%	17.5 mol%
3, R = Me	57:43	85:15	85:15	93:7
3, R = Ph	56:44	79:21	84:16	93:7
3, R = i-Pr	46:54	52:48	84:16	94:6
4, R = Me	57:43	27:73	27:73	9:91
4, R = Ph	58:42	52:48 [f]	16:84	6:94
4, R = i-Pr	55:45	50:50	26:74	8:92

[a] All product ratios determined by gas chromatography. [b] Carried out in anhydrous CH_2Cl_2 at 15 psi H_2 according to the general procedure described in Ref. 1b. [c] Carried out in anhydrous CH_2Cl_2 at 640 psi H_2 according to the general procedure described in Ref. 2. [d] Ref. 2 (640 psi H_2). [e] See Footnote 5. [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 = Me, Ph, i-C_3H_7) reveals that this catalyst stoichiometry effect on reaction diastereoselection exhibits significant substrate dependence. In addition, in all but one case (**4**, R = Ph)[5] the observed stereoselectivity was found to be independent of hydrogen pressure (15 - 1000 psi). Consequently, competing catalyst-promoted olefin isomerization (**3** $\rightleftarrows$ **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 hydrogen 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.[1b] The nature of this inverse relationship between catalyst concentration and reaction diastereoselection is quite intriguing. Crabtree has noted that $Ir(py)PCy_3^+$ is deactivated via the formation of a trinuclear bridged hydride which is inactive as a hydrogenation catalyst.[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.[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 $Ir(COD)py(PCy_3)PF_6$ (**2**).

Substrate	Product[a, b]	Mol % 2 $Ir(COD)py(PCy_3)PF_6$	Ratio Trans : Cis
		20.0 2.5	50:1 150:1
		20.0 2.5	33:1 [c] 52:1

[a] Carried out in anhydrous CH_2Cl_2 according to the general procedure provided in Ref. 1b. [b] All product ratios determined by capillary gas chromatography. [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]BF_4 (**7**) was prepared[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**, $Ir(DIPHOS\text{-}4)^+$ proved to be superior to the Crabtree catalyst $Ir(py)PCy_3^+$ but still less stereoselective than the rhodium analog $Rh(DIPHOS\text{-}4)^+$ (Table I).[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 $Ir(DIPHOS\text{-}4)^+$ (trans : cis = 20:1) than with $Ir(py)PCy_3^+$ (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.

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References and Notes.

(1) (a) Brown, J. M.; Naik, R. J. Chem. Soc. Chem. Commun. **1982**, 348.
(b) Stork, G; Kahne, D. E. J. Am. Chem. Soc. **1983**, 105, 1072.
(c) Crabtree, R. H.; Davis, M. W. Organometallics **1983**, 2, 681.
(d) Brown, J. M.; Hall, S. A. Tetrahedron Lett. **1984**, 26, 1393.

(2) Evans, D. A.; Morrissey, M. M. J. Am. Chem. Soc. **1984**, 106, 3866.

(3) NBD = norboradiene, DIPHOS-4 = 1,4-bis(diphenylphosphino)butane. NBD = norbornadiene, DIPHOS-4 = 1,4-bis(diphenylphosphino)butane. The detailed procedure for the preparation of **2** is provided in the supplementary material of Ref. 2. The complex, (Rh(COD)DIPHOS-4)BF_4, 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.

(4) Crabtree, R. H.; Felkin, H.; Fillebeen-Khan, T.; Morris, G. E. J. Organomet. Chem. **1979**, 168, 183. 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.

(6) Chodosh, D. F.; Crabtree, R. H.; Felkin, H.; Morris, G. E. J. Organometal. Chem. **1978**, 161, C67.

(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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