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HYDROXYL-DIRECTED HYDROGENATION OF HOMOALLYLIC ALCOHOLS. EFFECTS OF ACHIRAL AND CHIRAL RHODIUM CATALYSTS ON 1,3 STEREOCONTROL.

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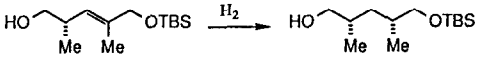
Abstract: The hydroxyl-directed hydrogenation of homoallylic alcohols is examined with cationic rhodium-(I) and iridium-(I) catalysts. These reactions proceed with high levels of diastereoselection when either $Rh(Diphos)^+$ or $Ir(pry)Pcy_3^+$ are employed as catalysts.

Recent studies from several research groups have established that the directed hydrogenation of hydroxy olefins presents considerable potential in stereoselective synthesis.[1] From the outset, this operation appeared to be an attractive method for relaying stereochemical information from hydroxyl-bearing stereocenters to prochiral olefinic centers via 1,2 and 1,3-asymmetric induction. While the former objective has repeatedly proven successful in a variety of cyclic and acyclic systems, the latter has received little attention, especially with acyclic hydroxy olefins. In this communication, we wish to disclose our results concerning the directed hydrogenation of acyclic homoallylic alcohols which proceed with high levels of 1,3 asymmetric induction. Although this study has primarily focused upon an examination of rhodium catalysts which have generally proven superior in other studies,[1b] comparative data for one iridium system has been included.

A series of substrates was examined to test the scope and limitations of catalyst directivity. The results of this study afford a number of significant observations. First, the hydrogenation of primary homoallylic alcohols substituted only at the allylic center proceed with high levels of diastereoselection resulting from hydroxyl direction (Table, Entries A-D). Both $Rh(Diphos\text{-}4)^{+2}$ and $Ir(pyr)Pcy_3^{+3}$ effectively catalyze this transformation and afford similar levels of diastereoselection under standard conditions (15 psi H_2, CH_2Cl_2, 25°C).[4] In these examples, the nonbonding interactions which restrict the hydroxyl moiety to the vicinity of one olefin face appear to result from strong A(1,3) allylic strain interactions.[5] Factors such as olefin geometry (Entry A vs. Entry B), steric requirements of the allylic substituent (Entry A vs. Entry C(D)), and relative stereochemistry between the allylic-homoallylic centers (Entry C vs. Entry D) have a small but noticeable effect on the reaction diastereoselection. Given the fact that such homoallylic alcohols afford good levels of directivity in the hydrogenation process, one may now confidently manipulate olefin geometry (cf. 1 vs. 2) or the directing hydroxyl function (cf. 3 vs. 4) to control the sense of asymmetric induction.

TABLE. HYDROXYL-DIRECTED HYDROGENATIONS OF HOMOALLYLIC ALCOHOLS.[a]

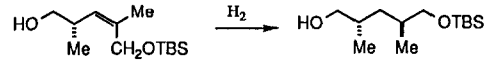
A



1

$Rh(Diphos\text{-}4)^+$	95:5
$Ir(pyr)Pcy_3^+$	73:27

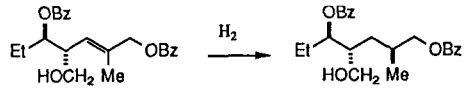
B



2

$Rh(Diphos\text{-}4)^+$	91:9

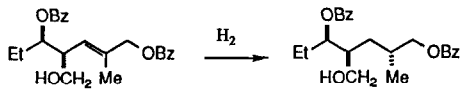
C



3

$Rh(Diphos\text{-}4)^+$	97:3
$Ir(pyr)Pcy_3^+$	97:3

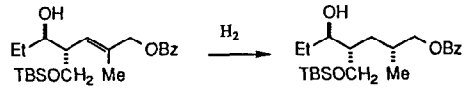
D



4

$Rh(Diphos\text{-}4)^+$	99:1
$Ir(Pyr)Pcy_3^+$	97:3

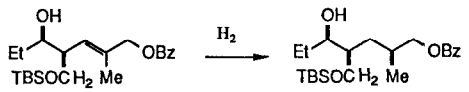
E



5

$Rh(Diphos\text{-}4)^+$	97:3
$Ir(pyr)Pcy_3^+$	94:6

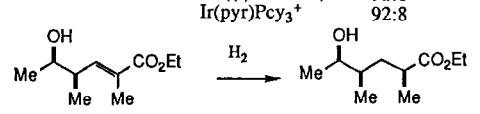
F



6

$Rh(Diphos\text{-}4)^+$	89:11
$Rh((+)\text{-}BINAP)^+$	97:3
$Rh((-)\text{-}BINAP)^+$	92:8
$Ir(pyr)Pcy_3^+$	92:8

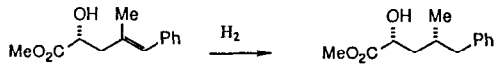
G



7

$Rh(Diphos\text{-}4)^+$	83:15
$Rh((+)\text{-}BINAP)^+$	98:2
$Rh((-)\text{-}BINAP)^+$	67:33

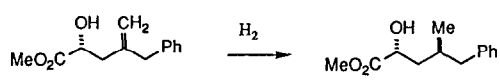
H



8

$Rh(Diphos\text{-}4)^+$	32:68
$Rh((+)\text{-}BINAP)^+$	55:45
$Rh((-)\text{-}BINAP)^+$	43:57
$Ir(pyr)Pcy_3^+$	67:33

I



9

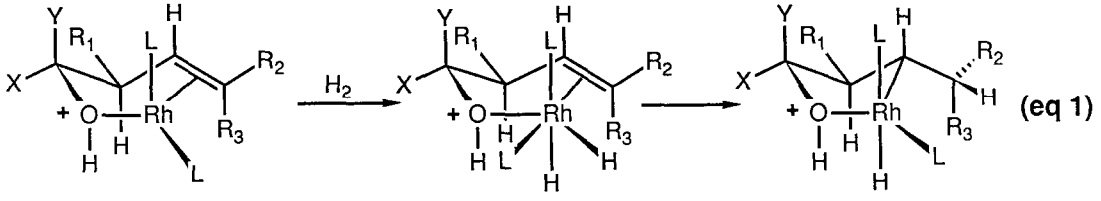
$Rh(Diphos\text{-}4)^+$	57:43
$Rh((+)\text{-}BINAP)^+$	80:20
$Rh((-)\text{-}BINAP)^+$	73:27
$Ir(pyr)Pcy_3^+$	79:21

[a] Substrates 3-9 were prepared in enantiomerically pure form. Satisfactory spectral data and elemental analyses were obtained on all compounds reported herein. All reactions proceeded in greater than 90% yield and product ratios were determined by capillary gas chromatography. Hydrogenations employing $Rh(Diphos\text{-}4)^+$ and $Ir(pyr)Pcy_3^+$ were conducted at 15 psi H_2 (CH_2Cl_2, 25 C) except for the $Rh(Diphos\text{-}4)^+$ hydrogenations in entries H and I. Hydrogenations employing the chiral rhodium BINAP catalysts were performed at 1000 psi H_2. Entry G was performed by Mr. Marcello DiMare. The abbreviation TBS found in the Table refers to the tert-butyldimethylsilyl moiety.

During the course of this study we have also had the opportunity to evaluate those substrates bearing asymmetric centers at both the allylic and carbinol carbons (Entries E-G). In these cases, where olefin isomerization is not an issue, both the rhodium and iridium catalysts (15 psi H_2, CH_2Cl_2, 25°C) afforded excellent levels of chirality transfer. In each of these reactions, the allylic stereocenter again defines the sense of asymmetric induction while the homoallylic carbinol center plays a subordinate role. In the three cases studied (Entries E,F,G), it appears that greater levels of asymmetric induction might be expected from the anti homoallylic alcohol diastereomer (Entry E). The lower levels of asymmetric induction provided solely by the homoallylic carbinol center with the achiral catalysts is also evident in the reduction of **8** and **9**.[6]

This study has also provided us with the opportunity to evaluate the influence of chiral catalysts on selected homochiral substrates. For example, the reaction diastereoselectivity in the hydrogenation of the syn homoallylic alcohols **6** and **7** may be significantly improved by employing the chiral Rh((+)-BINAP)$^+$ catalyst[7] (1000 psi H_2, CH_2Cl_2, 25°C)[8] in a double stereodifferentiating experiment.[9] It is noteworthy that both homoallylic alcohols **6** and **7** respond nicely to these chiral catalysts, even though the electronic nature of the olefins is considerably different. The sizeable increase in diastereoselection (0.8-1.2 kcal/mole) obtained from the chiral rhodium-(I) catalysts greatly extends the utility of this hydrogenation reaction.

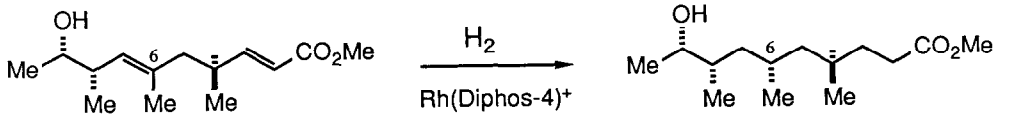
From the examples illustrated in the Table, a self-consistent rationale for the course of these reactions is proposed (eq 1).[10] The three stereochemically defined rhodium-substrate complexes, **A-C**, illustrated below are plausible intermediates in the production of the major hydrogenation product diastereomers (cf. Entries A-G). The minimization of the A(1,3) allylic strain interaction ($R_1 \rightleftharpoons R_3$) provides one of the the dominate conformational control elements in both **A** and **B**. These intermediates may also be used to rationalize why the anti homoallylic alcohol **5** exhibits higher reaction diastereoselectivity than the closely related syn cases **6** and **7**. In the former case (Entry E) the homoallylic substituent (X=Et) is disposed in the preferred pseudoequatorial conformation in both **A** and **B**. Conversely, the lower diastereoselectivity exhibited by the syn alcohols **6** and **7** correlates with the disfavored pseudoaxial orientation of the homoallylic substituent (Y=Et,Me) in rhodium complexes **A** and **B**. While this steric interaction between the homoallylic substituent and the catalyst ligand is significant, it does not appear great enough to render hydrogenation of substrates such as **8** and **9** synthetically useful.



(eq 1)

A **B** **C**

This methodology appears especially attractive for incorporation into the total synthesis of natural products due to the facility by which 1,3 stereochemical relationships are generated. For example, this directed hydrogenation concept has been employed in the synthesis of the C_1-C_{10} fragment of the ionophore ionomycin.[11] As shown below (eq 2), hydrogenation of homoallylic alcohol **10** catalyzed by Rh(Diphos-4)$^+$ (15 psi H_2, CH_2Cl_2, 25°C) afforded fully saturated hydroxy ester **11** as a 94:6 ratio of diastereomers at C_6 in 93% yield. The construction of this 1,3 dimethyl moiety, a prevalent structural feature in many polyether and macrolide antibiotics, serves to demonstrate the utility of this present methodology.



(eq 2)

10 **11**

Diastereoselection 94:6

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

(4) The hydrogenations shown in Entries A - G were conveniently run at atmospheric hydrogen pressure with Rh(Diphos-4)$^+$ (5-20 mol%) or Ir(pyr)Pcy$_3^+$ (2.5 mol%) without any observable olefin isomerization.

(5) Johnson, F. Chem. Rev. **1968**, 68, 375.

(6) Olefin isomerization was observed when **8** and **9** were hydrogenated with Rh(Diphos-4)$^+$ at atmospheric hydrogen pressure. This side reaction was not observed with Ir(pyr)Pcy$_3^+$. Additionally, in contrast to a earlier report (Ref. 1g) employing THF as solvent had no effect on the reaction diastereoselection.

(7) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. J. Am. Chem. Soc. **1980**, 102, 7932. We thank Dr. Larry Truesdale of Hoffmann-La Roche for supplying us with the optically pure BINAP ligands used in this study (+)-BINAP: $[\alpha]_D$ +214° (c 0.32, benzene), Lit. $[\alpha]_D$ +229° (c 0.32, benzene); (-)-BINAP: $[\alpha]_D$ -216° (c 0.32, benzene), Lit. $[\alpha]_D$ -229° (c 0.32, benzene).

(8) Hydrogenation of **6-9** with the chiral rhodium catalysts was extremely slow at atmospheric hydrogen pressure. High pressure hydrogenation conditions (1000 psi H_2) were employed to drive these reactions to completion. See reference 2c for precise experimental conditions for this reaction.

(9) Brown and Cutting (Ref. 1a) have recently reported a similar experiment involving a kinetic resolution of allylic alcohols.

(10) Similar substrate-metal organization has been proposed for the hydroxyl-directed epoxidation of homoallylic alcohols with V(+5) catalysts : Mihelich, E.D.; Daniels, K.; Eickhoff, D.J. J. Am. Chem. Soc. **1981**, 103, 7690.

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