RHODIUM-CATALYZED STEREOSELECTIVE HYDROFORMYLATION

Reported by Daniel Robbins October 16, 2008

INTRODUCTION

Hydroformylation, the conversion of olefins into aldehydes through the addition of CO and H_2, is an important industrial reaction that employs homogeneous catalysis by transition metals (Figure 1).[1] Hydroformylation is a valuable reaction in organic chemistry because it produces aldehydes, which are highly versatile chemical intermediates, uses readily available syngas as the primary reagent, is tolerant of many functional groups, and is atom efficient.[2,3,4] Cobalt complexes were initially used for hydroformylation, but more recently rhodium complexes have been implemented due to their higher activity under milder reaction conditions.[3] The hydroformylation of chiral olefin substrates allows for diastereoselective hydroformylation. Although the linear product is generally formed for most substrates, the branched product is chiral (R ≠ Me) and enantioselective hydroformylation is possible. Methods for Rh-catalyzed, diastereoselective and enantioselective hydroformylation reaction will be discussed.

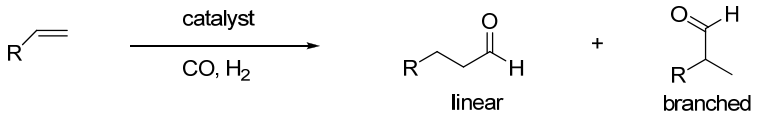
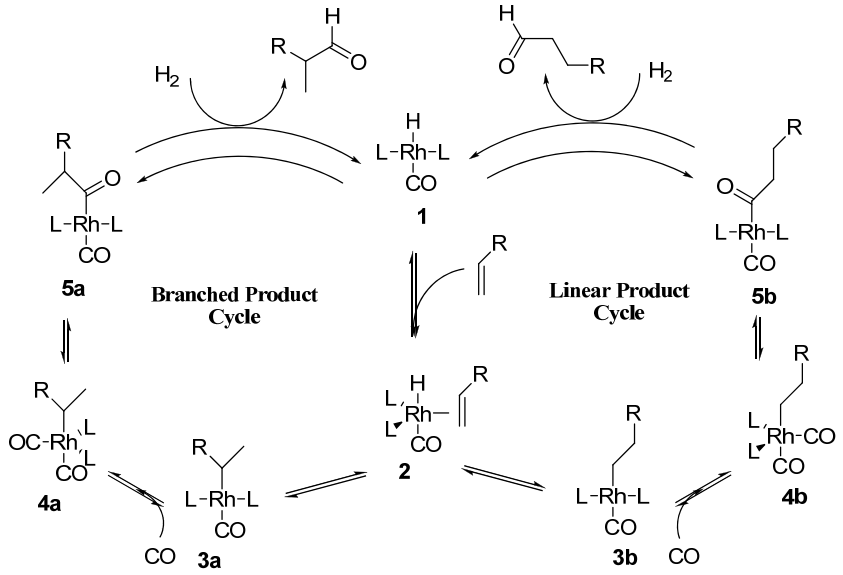


Figure 1. General Transformation for Hydroformylation.

BACKGROUND AND MECHANISM

The mechanism of hydroformylation follows the catalytic cycle initially described for cobalt catalysts in 1961 by Heck and Breslow.[5] Since that initial report, the hydroformylation mechanism has been studied for rhodium catalysts as well (Figure 2).[1,3] Beginning with a 16-electron Rh-H fragment (**1**), an olefin coordinates to an empty coordination site on Rh to form a 5-coordinate intermediate (**2**). Migratory insertion of the olefin into the Rh-H then gives a 4-coordinate Rh-alkyl compound (**3**), which coordinates a molecule of CO (**4**). Migratory insertion of the CO into the alkyl ligand then gives a Rh-acyl complex (**5**), which undergoes hydrogenolysis to give the aldehyde product and regenerate the Rh-H complex (**1**). Hydroformylation



can yield linear products, in which the olefin insertion step yields a primary alkyl ligand on Rh, or branched products, in which the olefin insertion step yields a secondary alkyl ligand on Rh. The olefin insertion step was shown to be a syn addition by stereochemical analysis of the hydroformylation of a trisubstituted olefin.[6] Thus, the hydrogen and formyl group are delivered to the same face of the carbon-carbon double bond.

CHEMOSELECTIVITY AND REGIOSELECTIVITY IN HYDROFORMYLATION

The control of chemoselectivity is a fundamental concern in Rh-catalyzed hydroformylation because branched and linear products can be formed.[3] The primary side reactions that occur during hydroformylation are Rh-catalyzed hydrogenation and isomerization of the olefin. Most Rh-phosphine or Rh-phosphite systems give high selectivity for hydroformylation. A notable exception is the hydroformylation of α, β-unsaturated ketones and aldehydes, for which olefin hydrogenation is seen exclusively.[7]

The control of regioselectivity is also a significant concern in hydroformylation. The primary factors that control the regioselectivity of hydroformylation are inherent substrate preferences, potential directing effects of functional groups appended to the substrate, and the effect of the catalyst.[3] Many substrates have a predisposed preference for a given constitutional isomer in hydroformylation. For monosubstituted olefins, alkyl substituents generally give a preference for the linear product when a Rh-phosphite catalyst is used.[8] Monosubstituted styrenes, however, give predominantly branched products.[9] This reverse in selectivity is generally attributed to the formation of an η^3-benzyl-Rh complex.[9] Electron-deficient olefins give branched products because of stabilization of the partial negative charge at the carbon bound to the metal.[10] 1,1-Disubstituted and trisubstituted olefins give linear aldehydes to avoid the formation of a quaternary center. Regioselective hydroformylation of unsymmetrical 1,2-disubstituted alkenes and the preferential formation of branched aldehydes from alkyl olefins are unsolved problems.[3]

However, certain substrates can be biased toward the preferential formation of a given constitutional isomer in hydroformylation through the action of directing groups. Krafft and coworkers have shown that amines can be used as directing groups for the formation of branched carbonylation products, which cyclize to form lactams.[11] Phosphines and phosphites can also be used as directing groups. The regioselectivity of hydroformylation can be reversed using this effect, as in the hydroformylation of 4-(diphenylphosphino)-1-butene. This compound would normally yield the linear aldehyde in the absence of the phosphine. The coordination of the Rh catalyst by the phosphine forms the favored 5-membered rhodacycle, which yields a branched aldehyde.[3]

Directing groups can also be used in substoichiometric quantities in directed hydroformylation. Breit and coworkers have shown that catalytic amounts of a phosphinite directing group can be used to effectively control regioselectivity.[12] In this reaction, homoallylic alcohols are converted to a phosphinite in situ and then cleaved via transesterification to regenerate the directing group (Figure 3). This method was shown to be useful for terminal and internal olefins and the product structure could be predicted by the preferred formation of a six-membered over a seven-membered ring chelate.[12] Homoallylic alcohols generally give the linear product, so this general method of regioselective, directed hydroformylation represents a strategy to override the inherent substrate bias.

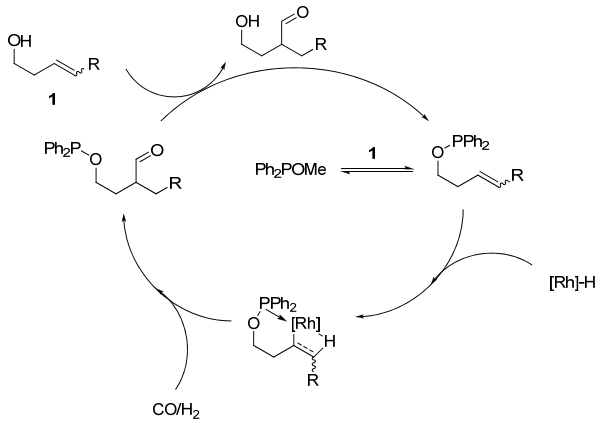


Figure 3. Proposed Mechanism of Phosphinite-directed Hydroformylation.

The regioselectivity of hydroformylation can be controlled through the design and modification of the catalyst. Casey and coworkers have studied the influence of various bidentate phosphine ligands on the distribution of branched and linear hydroformylation products.[13] These studies showed that the branched/linear ratio is determined by the migratory insertion of the olefin into the Rh-H to form a Rh-alkyl species and that this insertion is greatly influenced by the identity and orientation of the ligand. For bisphosphine ligands, two possible chelate orientations exist: diequatorial and axial-equatorial (Chart 1). Two ligands, DIPHOS (Figure 3), which gives an axial-equatorial orientation because of its bite angle (near 90°), and BISBI (Figure 3), which gives a diequatorial orientation because of its bite angle (near 120°), were chosen for this study. Chelating phosphines with larger bite angles, such as BISBI, express a significant preference for the linear aldehyde (b/l, 1:66) and chelating phosphines with small bite angles, such as DIPHOS, gave a small preference for the linear product (b/l, 1:2.6). This ability to affect different selectivity for the branched aldehyde illustrates the effect that design of the catalyst can have on the regioselectivity of the hydroformylation reaction.

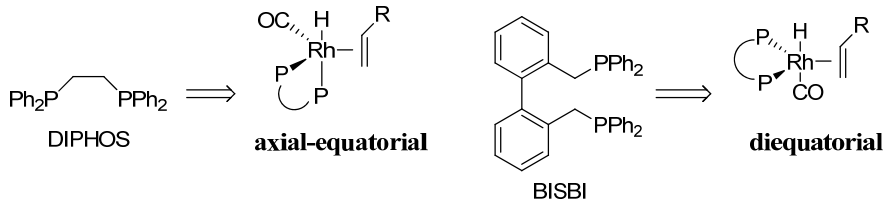
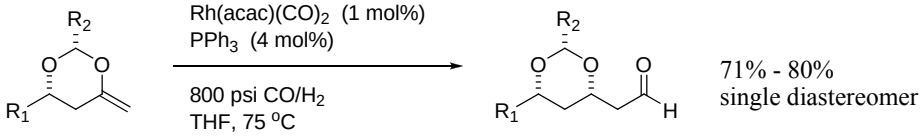


Chart 1. Bidentate Phosphine Ligands and Rh-complex Orientations.

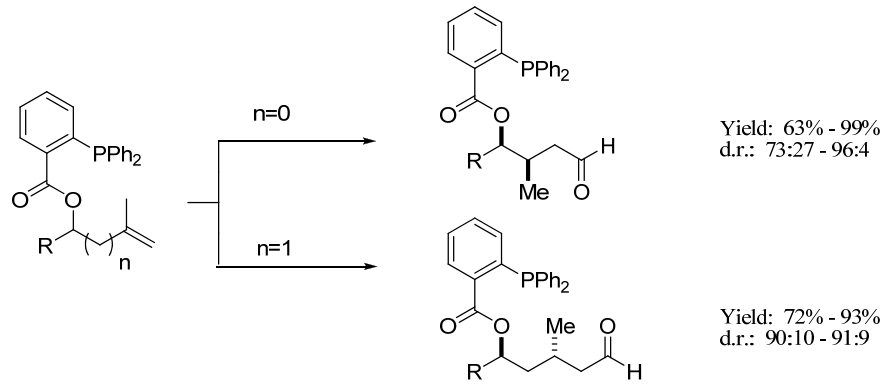
DIASTEREOSELECTIVE HYDROFORMYLATION

Diastereoselective hydroformylation allows for the formation of diastereomerically enriched aldehydes. Leighton has shown that the hydroformylation of cyclic enol acetals proceeds with very high regioselectivity and diastereoselectivity (Scheme 1).[14] The high diastereoselectivity in this reaction is attributed to a kinetic preference of olefin insertion dictated by the conformation of the ring. This transformation illustrates an alternative method for the synthesis of aldol fragments.



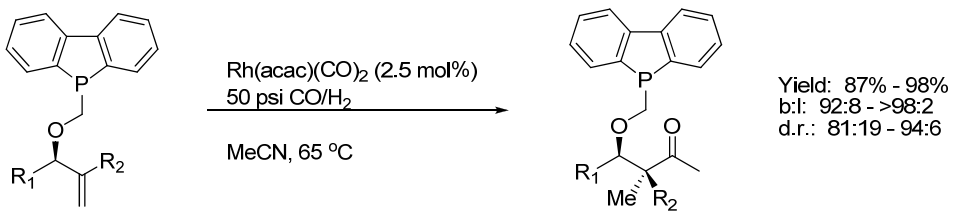
Scheme 1. Diastereoselective Hydroformylation of Cyclic Enol Acetals.

Diastereoselective hydroformylation can also be accomplished through the use of an appended directing group. Breit has demonstrated the diastereoselective hydroformylation of allylic and homoallylic alcohols that have been acylated with ortho-diphenylphosphinobenzoic acid (o-DPPB).[15] This directing group affords the aldehydes with very high diastereoselectivity (Scheme 2).



Scheme 2. Directed Diastereoselective Hydroformylation of Allylic and Homoallylic Alcohols.

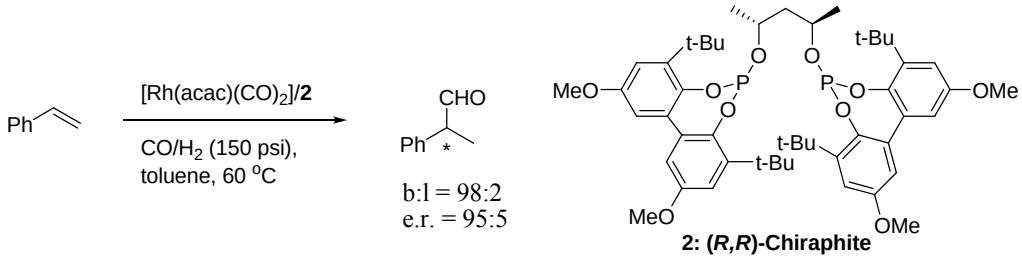
Diastereoselective hydroformylation with directing groups can also be used to override inherent substrate regioselectivity. This influence was demonstrated by Leighton through the use of a novel phosphine directing group (Scheme 3). This method allowed the synthesis of an aldol fragment with high regioselectivity, diastereoselectivity and yield.[16]



Scheme 3. Directed Diastereoselective Branched Hydroformylation of Allylic Alcohols.

ENANTIOSELECTIVE HYDROFORMYLATION

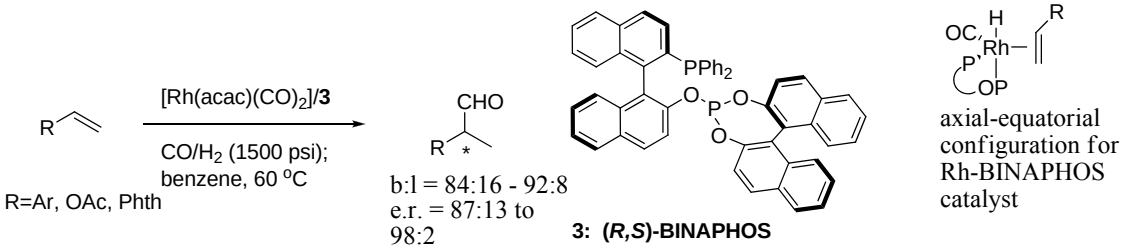
Enantioselective hydroformylation presents a significant challenge because the catalyst must simultaneously control regioselectivity and stereoselectivity. Early examples of enantioselective hydroformylation used Pt/Sn catalysts, but these catalysts suffered from poor regioselectivity and poor enantioselectivity, as well as competing olefin hydrogenation.[17] Initial reports of a Rh-DIOP catalyst gave low enantioselectivity and slow rates.[18] A significant breakthrough occurred when Babin and Whiteker introduced the diphosphite ligand Chiraphite for Rh-catalyzed asymmetric hydroformylation of styrene (Scheme 4).[1,19] These studies showed that the diphosphite ligand occupies a diequatorial orientation about the Rh center, and that this orientation was crucial for high enantioselectivity.[20, 23] On the basis of these studies, the Chiraphite ligand was further modified by Bakos and van Leuween by adjusting the size of the aryl substituents and examining the reactivity of different diastereomers of the chiral ligand. These studies yielded catalysts with improved reaction rates and comparable enantioselectivity.[21]



Scheme 4. Asymmetric Hydroformylation of Styrene with Rh-Chiraphite.

Another significant breakthrough in enantioselective hydroformylation was the development of the Rh-BINAPHOS catalyst by Takaya.[22] Olefins substituted with electron-withdrawing groups gave strong preference for the branched product with high enantioselectivity (Scheme 5). Mechanistic studies of the Rh-BINAPHOS system yielded important information about the mechanism and sense of asymmetric induction.[23] In the trigonal bipyramidal Rh complex, the two carbon monoxide ligand and the phosphine are in equatorial positions and the phosphite and hydride are in axial positions (Figure 8). This single conformation is crucial for high enantioselectivity because the ligand does not have C_2

symmetry. Through modifications of BINAPHOS, the origin of stereocontrol is the binaphthyl phosphine segment of the ligand.



Scheme 5. Asymmetric Hydroformylation with Rh-BINAPHOS.

Since the introduction of the Rh-BINAPHOS system, several other phosphite and phosphine ligands have been developed for asymmetric hydroformylation.[24] Several bisphosphite ligands have been developed based upon the Kelliphite structure (shown below).

These ligands give good regioselectivity and enantioselectivity for allyl cyanide and vinyl acetate, but poor selectivity and yield for styrene.[25] The effect of different ligand structure has a significant effect on regioselectivity and enantioselectivity. Klosin, Whiteker and coworkers have synthesized a series of Kelliphite derivatives and shown that small bite angles for the diphosphite ligands lead to higher enantioselecivity.[26]

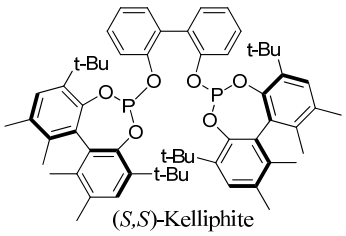
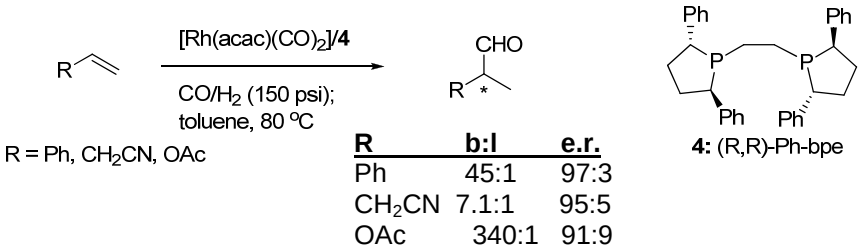


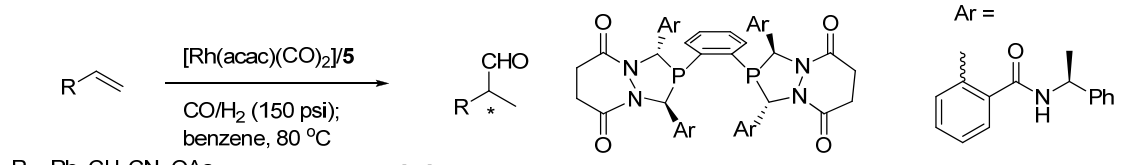
Figure 3. Structure of (*S,S)*-Kelliphite.

Following the successful development of bisphosphite and phosphine-phosphite ligands, bisphosphine ligands have also been developed for asymmetric hydroformylation. Klosin and coworkers showed that a Rh-Ph-bpe system is highly effective for the asymmetric hydroformylation of styrene, vinyl acetate and allyl cyanide.[27] This catalyst gave good regioselectivity, good enantioselectivity and high turnover number (Scheme 6).



Scheme 6. Asymmetric Hydroformylation with Rh-Ph-bpe.

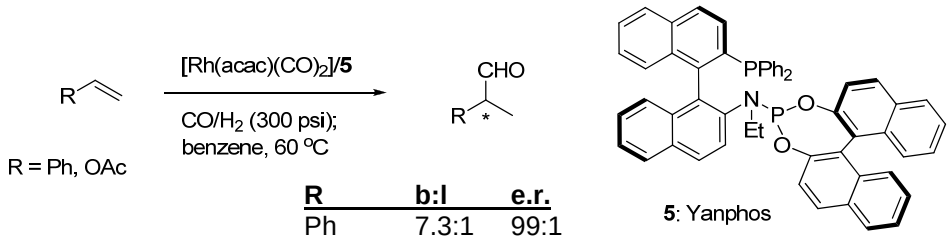
Landis and coworkers have developed diazaphospholanes for asymmetric hydroformylation.[28] These ligands were shown to give good regioselectivity and good enantioselectivity over a range of substrates with good rates and low catalyst loadings (Scheme 7).[28]



R	b:l	e.r.
Ph	6.6:1	91:9
CH_2CN	4.1:1	94:6
OAc	37:1	98:2

Scheme 7. Asymmetric Hydroformylation with Rh-diazaphospholane Catalyst.

A modified BINAPHOS hybrid phosphite-phosphoramidite ligand was developed by Zhang for asymmetric hydroformylation (Scheme 8). This ligand, a slight modification of BINAPHOS gave high enantioselectivity and moderate regioselectivity for the hydroformylation of styrene and vinyl acetate.[29] Phosphites offer a comprehensive set of ligands for the three primary substrates examined, as Chiraphite gives good selectivity for styrene, whereas Kelliphite gives good selectivity for vinyl acetate and allyl cyanide.



R	b:l	e.r.
Ph	7.3:1	99:1
OAc	13.3:1	98:2

Scheme 8. Asymmetric Hydroformylation with Rh-phosphine-phosphoramidite (YanPhos).

The Rh-YanPhos catalyst is the most effective catalyst for enantioselective hydroformylation due to its consistently high reactivity and enantioselectivity as well as a wide substrate scope.

CONCLUSION

Hydroformylation is a useful and powerful tool because the construction of aldehydes from olefins, CO and H_2 has tremendous synthetic potential. Models for control of regioselectivity in hydroformylation for several substrate classes are well-established and several strategies exist to override substrate bias. Developments in stereoselective hydroformylation have enabled the introduction of the formyl group with predictable stereocontrol. The development of enantioselective hydroformylation has illustrated the use of phosphites as ligands and the development of the Rh-BINAPHOS catalyst illustrated the use of C_1-symmetric ligands in asymmetric catalysis.

Stereoselective hydroformylation allows for an alternative method for the synthesis of several common subunits, such as aldol fragments and α-aryl aldehydes, which can also be formed by the cross-coupling of aldehydes and aryl halides.[30] Stereoselective hydroformylation also gives versatile aldehydes that can be easily converted to carboxylic acids through oxidation or to alcohols through reduction. Despite its demonstrated utility, the use of hydroformylation in the production of fine chemicals or in total synthesis is still quite limited. Further studies into the source of asymmetric induction in various classes of catalysts should give insight into mechanism of these reactions and provide the theoretical foundation necessary for the rational design of new hydroformylation catalysts. The development of improved hydroformylation catalysts will encourage its use in a multitude of practical chemical applications.

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