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Possible Origin of Electronic Effects in Rh(I)-Catalyzed Enantioselective Hydrogenation

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Enantioselective hydrogenation of olefins is one of the most reliable and practical asymmetric methods for introducing chiral centers,[1] yet synthetic chemists are often puzzled by poor enantioselectivity obtained with a particular substrate. Notably, asymmetric hydrogenation of olefins lacking attached chelating groups had remained an unsolved problem until recent remarkable progress reported by Pfaltz.[2] Evidently, further efforts are needed to understand how chiral induction occurs in asymmetric hydrogenation to provide guidance in designing more general and effective catalysts.[3]

The isolation of the first metal-alkyl intermediates of the hydrometalation step by Halpern and Brown paved the way for mechanistic investigation into asymmetric hydrogenation.[4] Halpern's kinetic studies with MAC[3a] showed that oxidative addition of H_2 onto the diastereomeric olefin-bound Rh(I) catalysts is the rate-determining and enantioselection step; the isolation of the dihydride intermediate by a parahydrogen-induced polarization (PHIP) technique,[5] as well as a theoretical study,[5b] however, suggest the hydrometalation step could also be the rate-determining step that affects the chiral induction. To date, rationalization of chiral induction and design of improved chiral ligands for hydrogenation are often based on steric arguments. On the other hand, electronic effects with respect to both substrates and ligands are less thoroughly understood. The most unambiguous evidence of electronic effects in asymmetric hydrogenation was obtained by RajanBabu and Ayers by investigating Rh(I) catalyzed hydrogenation of the extensively studied substrates dehydroamino acids.[6,7] In this case, a drastic decrease of *ee* was observed when electron-deficient ligands were employed (Figure 1). The origin of this effect is attributed to the alteration of the relative rates of oxidative addition of H_2 to the diastereomeric $L_2Rh(I)$−olefin complexes.

Herein we disclose our findings in support of a new model rationalizing the electronic effects in enantioselective hydrogenation: electronic properties of the catalysts and substrates affect the regioselectivity of hydrometalation and hence the enantioselectivity. This model, in conjunction with Knowles' "four quadrant steric analysis"[1a] for the asymmetric reduction of a pro-chiral alkene, explains how electronic effects could determine to which face of the olefin the metal hydride adds. Since the chiral ligands are attached to the metal, we argue that the switch in the regioselectivity of hydrometalation from pathway **A** to **B** will position the chiral ligand at the different end of the double bond, which will inevitably affect enantioselection of the *re*-face and *si*-face of the olefins based on Knowles' four quadrant model (Figure 2). Importantly, if the sense of chiral induction in path **A** and **B** are opposite, their simultaneous participation in the same reaction could result in erosion of enantioselectivity. This is also consistent with the high enantioselectivity often obtained with functionalized substrates where regioselective hydrometalation assisted by σ-chelation is made possible.[4,7]

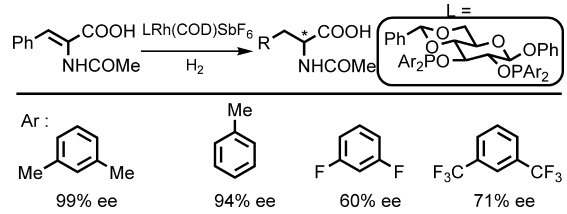

Figure 1. Electronic effects observed by RajanBabu and Ayers.

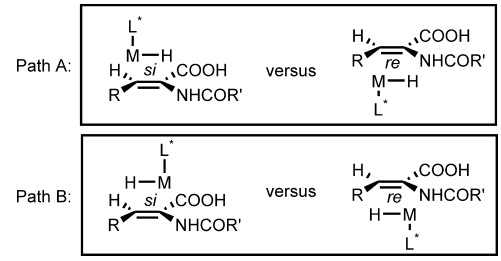

Figure 2. Effects of regioselectivity on enantioselection.

As the first key step to verify this model, we sought to determine how electronic properties of catalysts influence the regioselectivity of the hydrometalation step. A convenient method for determining regioselectivity of hydrometalation has been previously developed by Spencer using the location of deuterium incorporation into *cis*-β-methoxystyrene **1** as a reporter (Table 1; for the measurement and calculation of D-incorporation see SI).[8] Notably, other deuterium labeling strategies have been widely used in hydrogenation.[9] Our experimental efforts began with the preparation of catalysts with systematically tuned electronic properties following a literature procedure[10] (Table 1). Remarkably, deuteration of *cis*-β-methoxystyrene **1** using these catalysts under 1 atm of D_2 showed, for the first time, that reduction of the electronic density of the ligands can switch the regioselectivity of hydrometalation from mode **a** to mode **b** (Table 1) consistently.

This result encouraged us to electronically tune the most broadly used BINAP ligands[1b] in the same manner and test how this could influence the enantioselectivity. Based on analysis depicted in Figure 2, we anticipate a drastic change in *ee* values including a possible switch of the sense of chiral induction by tuning the electronic properties of BINAP ligands. Thus a range of ligands with different electronic properties are prepared using methods developed in our laboratory (Table 2).[11]

The most extensively studied substrate dehydrocinnamic acid **3** and its derivatives were selected for the investigation. The enantioselectivity of asymmetric hydrogenation of substrates **3** and **4** suffered a drastic drop from 88% and 90% *ee* (Table 2, entries 1, 2) to 45% and 13% *ee*, respectively, when electron-deficient catalyst **2c** was used (entries 9, 10). Following the trend of regioselectivity observed in Table 1, a

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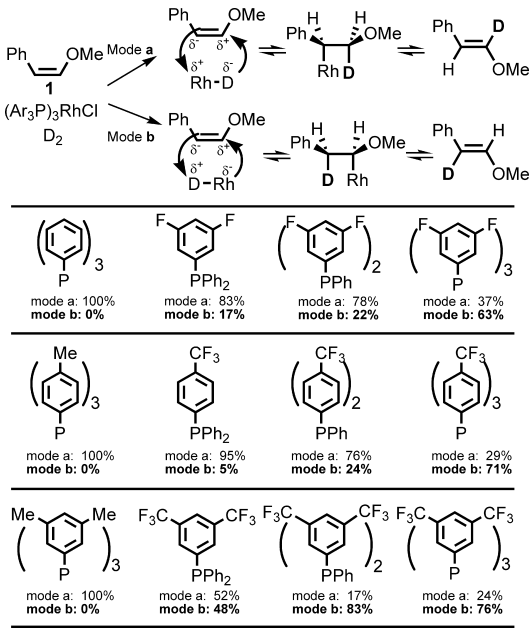
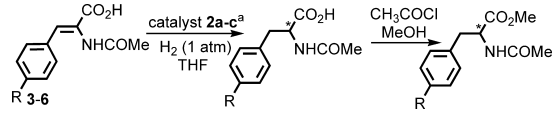
Table 1. Electronic Effects on the Regioselectivity of Hydrometalation[a]



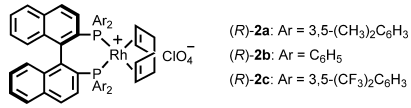
[a] Reaction conditions: $(Ar_3P)_3RhCl$ (0.025 mmol), *cis*-β-methoxystyrene (0.5 mol), 1 atm of D_2, in benzene at 24 °C, 0.5−5 h.

Table 2. Reversing the Enantioselectivity *via* Electronic Tuning



entry	catalyst	substrate	yield (%)	e.e.	configuration
1	(*R*)-**2a** [b]	**3** (R=CF_3)	95	88	*S*
2	Ar = 3,5-$(CH_3)_2C_6H_3$	**4** (R=H)	98	90	*S*
3		**5** (R=Me)	90	67	*S*
4		**6** (R=OMe)	76	62	*S*
5	(*R*)-**2b**	**3** (R=CF_3)	96	76	*S*
6		**4** (R=H)	98	84	*S*
7	Ar = C_6H_5	**5** (R=Me)	92	55	*S*
8		**6** (R=OMe)	76	48	*S*
9	(*R*)-**2c**	**3** (R=CF_3)	80	45	*S*
10	Ar = 3,5-$(CF_3)_2C_6H_3$	**4** (R=H)	82	13	*S*
11		**5** (R=Me)	68	5.5	***R***
12		**6** (R=OMe)	58	19	***R***

[a] Catalysts: Rh(BINAPs)(COD)ClO_4 (BINAPs = 2,2′-bis(diarylphosphino)-1,1′-binaphthyl). [b] General reaction conditions: dehydrocinnamic acid (0.2 mmol), catalyst (0.01 mmol), 1 atm of H_2, in THF at 24 °C. When (*R*)-**2a** was used, reactions were carried out at 60 °C to enhance the reactivity.



shift of the hydrometalation regioselectivity from predominantly mode **a** to a mixture of mode **a** and mode **b** is expected. This shift could result in erosion of enantioselectivity due to two possible causes: (1) the chiral induction in mode **b** is less effective based on a steric argument; (2) the sense of chiral induction in mode **b** is opposite to that in mode **a**; therefore, the operation of mode **a** and mode **b** simultaneously will decrease *ee*.

Further experiments are carried out to to gain insights into the sense of chiral induction in the mode **b** pathway. According to our previous studies, electron-donating groups attached to the aryl rings of substrates further enhance mode **b** hydrometalation as a result of the polarity of the double bonds.[8] If mode **b** hydrometalation can be further promoted to operate as a predominant pathway by using these types of substrates, the sense of chiral induction of mode **b** can then be revealed. As anticipated, the hydrogenation of **5** and **6** using electron-deficient catalyst **2c** afforded enantioselectivity in favor of (*R*)-configuration, suggesting a reversal of the sense of chiral induction. The relatively low *ee* is most likely due to the simultaneous operation of the mode **a** pathway giving the opposite chiral induction. While we cannot rule out the possibility that the weakened coordination of catalyst **2c** could lead to background reaction[7] and result in the decrease of *ee*, the reversed sense of chiral induction is more consistent with our mechanistic model. At this stage, these analyses are not conclusive partially due to the lack of experimental tools to determine regioselectivity and enantioselectivity using the same set of olefin substrates and chiral ligands.

In summary, we have shown that the electronic density of Wilkinson-type catalysts strongly influences the regioselectivity of the hydrometalation step. Tuning electronic properties of BINAP type chiral ligands in asymmetric hydrogenation result in a drastic decrease or even reversal in chiral induction. These two observations, being consistent with each other, point to a new direction to seek the origin of electronic effects in asymmetric hydrogenation.

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Supporting Information Available: Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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