Reversal of Enantioselectivity in the Asymmetric Rhodium- versus Iridium-Catalyzed Hydroboration of Meso Substrates

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Since Männig and Nöth first reported the transition-metal-catalyzed hydroboration,[1] increasing attention has been paid to the development of this new reaction, especially in the field of asymmetric catalysis.[2] It was found that chemo-,[1] regio-,[3] and diastereoselectivities[4] could be obtained opposite to the uncatalyzed processes. Furthermore, besides the access to enantiopure alcohols or amine derivatives, the transmetalation of the intermediate boronic esters to the corresponding organozinc derivatives considerably broadens the scope of the rhodium-catalyzed hydroboration.[5] However, applications of this promising reaction have been restricted to a limited number of substrates; only successful enantioselective hydroboration of styrene and its derivatives (ee > 95%), and norbornene in a lesser extent (ee = 84%), have been reported.[2] Despite intensive work, no other metallic substitute for rhodium has been reported to be effective in such an asymmetric transformation. Moreover, improvement of this process is hampered by the understanding of its mechanism, which is rather vague.[6] Herein we report the first example of asymmetric iridium-catalyzed hydroboration. We also bring new insight into the catalytic cycle of this reaction.

Recently, we have developed a straightforward access to polysubstituted diaminocyclopentanes **3** based on the desymmetrization of meso bicyclic hydrazines **1** via rhodium-catalyzed asymmetric hydroboration (Figure 1).[7]

Although very few examples of racemic iridium-catalyzed hydroborations have been reported and the reaction with endocyclic alkenes is believed to be very sluggish,[8] the enhanced reactivity of our substrates as compared to norbornene prompted us to test iridium catalysts with this series (Table 1). Using our previously established hydroboration conditions, we were pleased to see that alcohol **2a** could be obtained with 1 mol % of [Ir(COD)Cl]₂ as the iridium source (entry 2). A higher chemical yield could be achieved using the same amount of precatalyst loading by increasing the reaction duration (entry 3). Reaction at room temperature with DIOP as a ligand could afford compound **2a** in 40% yield with 44% ee (entry 5). These results show for the first time that, despite a lower reactivity, neutral iridium complexes can catalyze asymmetric hydroboration. More interestingly, a *complete reversal of enantioselectivity* was observed between Rh and Ir systems. This phenomenon appeared as a general feature because it was observed on all substrates and conditions studied (Scheme 1).

To our knowledge, reversal of enantioselectivity in the course of an asymmetric reaction catalyzed by two transition metals having the same d shell electronic configuration is unprecedented.[9] This observation brings new information on the mechanism of hydroboration. Two main catalytic cycles, based on experimental and theoretical studies, have been proposed (Figure 2).[6b] While several
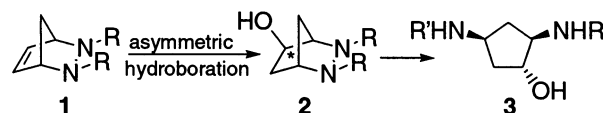
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Figure 1. Desymmetrization of meso hydrazines.

Table 1. Rhodium- versus Iridium-Catalyzed Hydroboration of Compound **1a**; Influence of Ligand

| entry	L*	solvent T(°C) (t[h])	M	yield (%)[a]	er[b]
1	(S,S)-BDPP	DME, −50 (0.5)	Rh	91	92:8[c]
2	(S,S)-BDPP	DME, 0 to room temp (0.5)	Ir	7	32:68
3	(S,S)-BDPP	DME, 0 to room temp (7)	Ir	30	34:66
4	(S,S)-DIOP	DME, −50 (0.5)	Rh	46	23:77
5	(S,S)-DIOP	DME, room temp (7)	Ir	40	72:28
6	(R)-quinap	DME, −50 (0.5)	Rh	11	62:38
7	(R)-quinap	THF, room temp (7)	Ir	27	44:56

[a] Yield of analytically pure compound. [b] Determined by chiral HPLC. [c] The absolute configuration of the major enantiomer has been established to be (1R,4R,5R) (see ref 7).

authors describe a key step involving a migratory insertion into the metal−H bond,[10] others favor the migration of a boryl group.[11] If the insertion step is the determining one in the cycle, these two pathways should lead to opposite regioisomers or, in the case of meso substrates, enantiomers.

The possible substrate-dependent reversibility of this step complicates the analysis.[10] In our case, we have a dramatic acceleration of the hydroboration with bicyclic hydrazines as compared to the norbornene case. This can be explained by the stabilization of the transition state of the migratory insertion by two σ*-nitrogen lone pair interactions, and it suggests that this is the first irreversible step in the cycle (Figure 3).[12]

Thus, solvent- and ligand-dependent stereoselectivity can be explained by means of the difference in diastereomeric transition states energetic levels (TS₁ versus TS₁′ and TS₂ versus TS₂′), and systematic reversal of enantioselectivity (regioselectivity) is likely to be the result of two different insertion pathways (TS₁ versus TS₂ and TS₁′ versus TS₂′). Theoretical studies on bond dissociation energies have shown that insertion into the Ir−Bcat bond is favored by 8 kcal mol⁻¹ over the insertion into the Ir−H bond.[13] In the case of our substrates, we can propose that this pathway is involved with [Ir(COD)Cl]₂ and that the use of [Rh(COD)Cl]₂ involves a key Rh−H migratory insertion step.
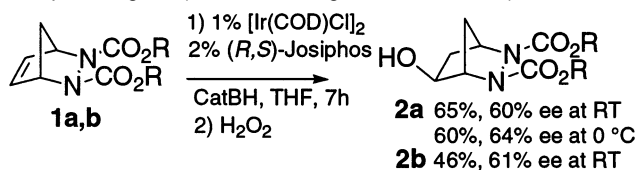
Scheme 1. Rhodium- versus Iridium-Catalyzed Hydroboration (Absolute Configurations Not Determined)[a]

M = Rh : er = 10:90
M = Ir : er = 29:71

M = Rh : er = 20:80
M = Ir : er = 58:42

M = Rh : er = 13:87
M = Ir : er = 59:41
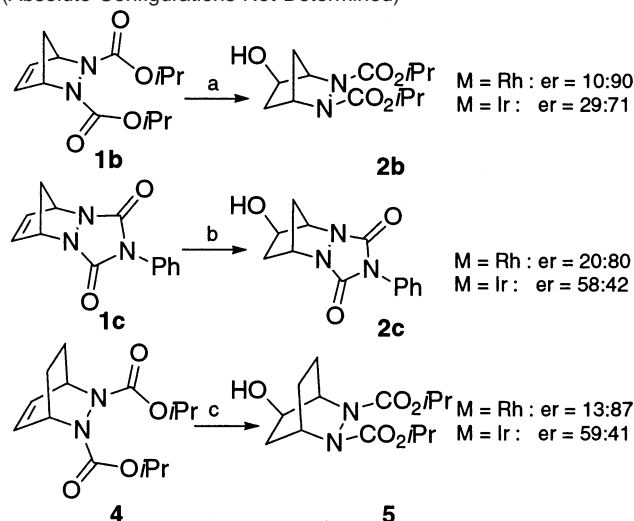
[a] Reagents and conditions: (a) M = Rh, 1% [Rh(COD)Cl]$_2$, 2% (S,S)-BDPP, CatBH (2 equiv), DME, −50 °C, 0.5 h, then H$_2$O$_2$, 50%. M = Ir, 1% [Ir(COD)Cl]$_2$, (S,S)-BDPP, CatBH (2 equiv), THF, room temperature, 7 h, then H$_2$O$_2$, 26%; (b) M = Rh, 1% [Rh(COD)Cl]$_2$, 2% (S,S)-BDPP, CatBH (2 equiv), DME, −50 °C, 0.5 h, then H$_2$O$_2$, 78%. M = Ir, 1% [Ir(COD)Cl]$_2$, (S,S)-BDPP, CatBH (2 equiv), THF, room temperature, 7 h, then H$_2$O$_2$, 9%; (c) M = Rh, 1% [Rh(COD)Cl]$_2$, 2% (S,S)-BDPP, CatBH (2 equiv), DME, −50 °C to room temperature, 7.6 h, then H$_2$O$_2$, 68%. M = Ir, 10% [Ir(COD)Cl]$_2$, (S,S)-BDPP, CatBH (2 equiv), THF, room temperature, 7 h, then H$_2$O$_2$, 17%.
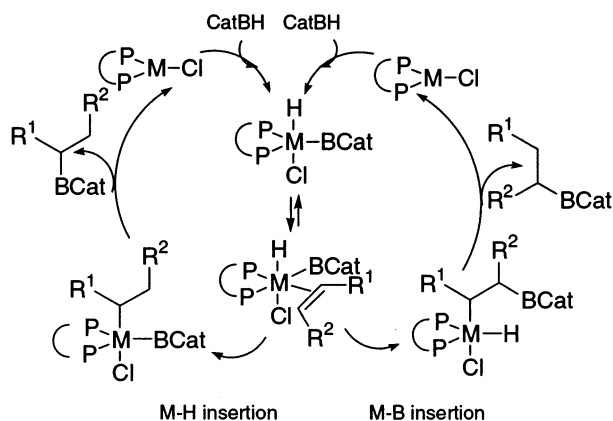
Figure 2. Simplified postulated catalytic cycles for hydroboration.
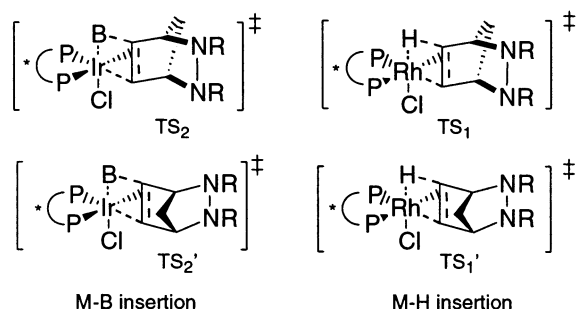
Figure 3. Possible transition states for the migratory insertion steps. Some groups have been omitted for clarity.

Finally, chemical yield and enantioselectivity of Ir-based desymmetrization were increased by using commercially available (R,S)-Josiphos ligand, leading to alcohols **2a,b** in 46−65% yield

Scheme 2. Iridium-Catalyzed Hydroboration with Ferrocenyl Phosphine Ligand (Absolute Configuration: 1S,4S,5S)

1) 1% [Ir(COD)Cl]$_2$
2% (R,S)-Josiphos

CatBH, THF, 7h

2) H$_2$O$_2$

2a 65%, 60% ee at RT
60%, 64% ee at 0 °C

2b 46%, 61% ee at RT

with ee up to 64% (Scheme 2). These promising results might be improved by a fine electronic tuning of ferrocenyl phosphines or P,N ligands.[14]

In summary, we have reported the first Ir-catalyzed asymmetric hydroboration with ee and chemical yields up to 64%. We have also shown an unprecedented reversal of enantioselectivity for a catalytic desymmetrization reaction by exchanging two transition metals having the same d shell electronic configuration. These results helped us to show that, at least on our substrates, Rh-catalyzed hydroboration involves a metal−H insertion, and a boryl migration is involved when using an Ir precatalyst. More generally, the use of meso substrates, leading to enantiomers instead of regioisomers, avoids the introduction of thermodynamic bias for regioselectivity and could be a general tool for the investigation of these kinds of problems.[15]

Supporting Information Available: Experimental procedures and analytical data for ee determination (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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