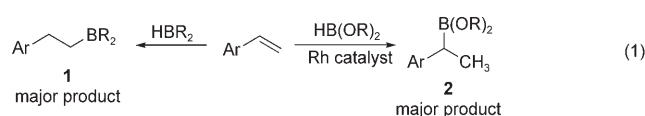


Regioselectivity of the Rhodium-Catalyzed Hydroboration of Vinyl Arenes: Electronic Twists and Mechanistic Shifts**

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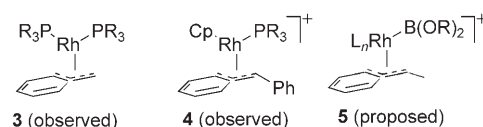
In memory of Yoshihiko Ito

The hydroboration of alkenes represents a versatile synthetic method for the functionalization of organic compounds.^[1] The installed carbon–boron bond can be converted into C–O, C–N, and C–C bonds with retention of stereochemistry.^[1b] Several highly enantioselective catalysts have been developed by the groups of Hayashi,^[2] Brown,^[3] Knochel,^[4] Togni,^[5] and Takacs^[6] among others, allowing the hydroboration to be employed in the preparation of a variety of organic compounds including NSAIDs (non-steroidal anti-inflammatory drugs), such as Ibuprofen and Naproxen.^[7] Remarkably, not only does the catalyst affect the introduction of asymmetry, it can also alter the chemo- and regioselectivity of the reaction.^[1,8] For example, the uncatalyzed hydroboration of styrene with reagents such as 9-BBN occurs with formally anti-Markovnikov selectivity yielding linear borane **1**. Conversely, the rhodium-catalyzed reaction affords predominantly regioisomer **2** with up to 99 % selectivity.^[2]



However, the branched selectivity observed in this catalyzed reaction occurs with only a few types of olefins, among which vinyl arenes are the most prominent.^[1,8] In the case of simple aliphatic olefins, linear selectivity or even “chain running”, where internal olefins are isomerized to the corresponding terminal isomer prior to hydroboration^[9] can be observed. The branched selectivity observed with vinyl arene substrates is of particular interest since a chiral product

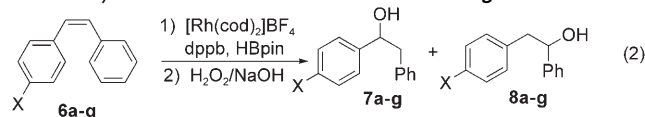
is generated. This unique regioselectivity has been attributed to the stabilizing effect of a π -benzyl interaction available only to the branched isomer **3**.^[2] π -Benzyl complexes of a



variety of transition metals^[10–15] including rhodium^[16–21] have been isolated, however, there is no empirical evidence to definitively ascribe the regioselectivity in the rhodium-catalyzed hydroboration to this interaction.

In order to probe the importance of π -benzyl interactions in the regiodefining event of the hydroboration reaction, we carried out hydroborations of mono-*para*-substituted *cis*-stilbenes **6a–g** (Table 1).^[22] Only *para*-substituted stilbenes

Table 1: Hydroboration of *cis*-stilbene derivatives **6a–g**.^[a]



Substrate, X	σ	Ratio 7/8	Yield [%] ^[b]	Mass balance [%] ^[b]
6a , CF ₃	0.54	3.00:1	67 (63)	93 (87)
6b , Cl	0.23	1.63:1	43 (43)	87 (97)
6c , F	0.06	1.12:1	78 (86)	99 (94)
6d , Me	−0.17	1.10:1	49 (49)	91 (96)
6e , OMe	−0.27	1.20:1	81 (78)	90 (95)
6f , OiPr	−0.29	1.25:1	61 (59)	98 (91)
6g , NMe ₂	−0.83	1.89:1	18	50

[a] See Experimental Section for details; dppb = 1,4-bis(diphenylphosphanyl)butane. [b] Determined by ¹H NMR spectroscopy versus internal standard, yields of isolated product in parentheses.

were employed to prevent complications due to steric effects. Remarkably, we found that regioisomer **7**, in which boron was placed proximal to the substituted aryl ring, was preferred in all cases, regardless of whether the substituent was electron-donating or electron-withdrawing.

The hydroboration reaction was carried out using pinacol borane (HBPin) as the hydroborating reagent on mono-*para*-substituted geometrically pure *Z*-stilbenes **6a–g** (Table 1). Following oxidation with hydrogen peroxide, the resulting alcohols were isolated by column chromatography as mix-

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tures of isomers.^[23] The identities of the individual regioisomers were verified by comparison to authentic samples prepared by Grignard addition to the requisite aldehydes.

With the one exception of *p*-dimethylamino stilbene, the reactions were quite clean with mass balances generally exceeding 90%.^[24] Recovered starting material was always devoid of the *cis* isomer, presumably due to a concurrent isomerization to the more stable *trans* isomer.

As previously noted, the major isomer always corresponded to borylation proximal to the substituted aromatic ring, irrespective of the electronic influence of the *para*-substituent. The greatest selectivity was observed for the most electron-donating, NMe₂, and most electron-withdrawing, CF₃, *para*-substituents. A graph of log(isomer ratio) versus σ revealed a linear free energy relationship with a minimum centered at the origin (Figure 1). Hammett plots such as this

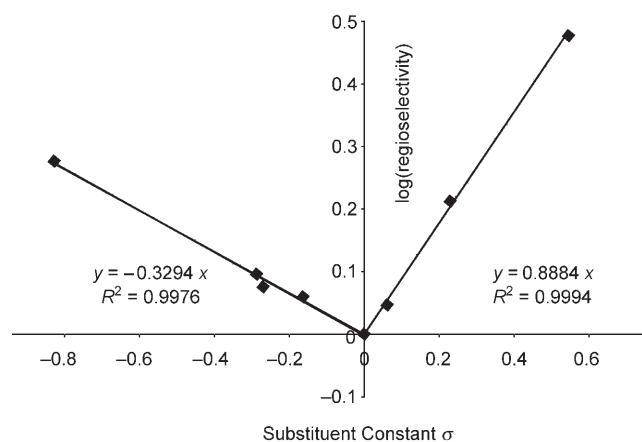


Figure 1. Hammett plot for unsymmetrically substituted stilbenes.

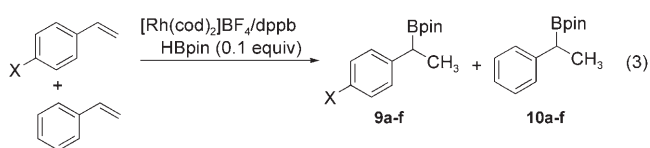
featuring a minimum are usually interpreted as resulting from a competition between two mechanisms, one favoured by electron-donating, and the other by electron-withdrawing substituents.^[25,26] Interestingly, in this case, the two different mechanisms lead to the preferential formation of the same regioisomer.

As shown in Figure 1, the correlation coefficients for the Hammett plots were very high (0.998 and 0.999) indicating that the fit to the linear regression is good in both cases. The data were also analyzed using σ^+ and σ^- parameters, but the best correlation was observed using the original Hammett σ parameter.

The hydroboration of similar unsymmetrical stilbenes with catechol borane (HBCat) in place of pinacol borane using quinap (1-(2-diphenylphosphanyl-1-naphthyl)isoquinoline) as the ligand has been recently reported by Brown et al. to give hydroboration proximal to the less electron-rich arene in all cases.^[22,27,28] We believe this stems from significant mechanistic differences between hydroborations with HBCat and HBPIn.^[29]

In addition to stilbene derivatives, we examined the reaction of styrenes, which are more common hydroboration substrates. In this case, intermolecular competition experiments were carried out in which equimolar amounts of

styrene and *para*-substituted styrene derivatives were exposed to a limiting amount of HBPIn, Equation (3). This



study provides information about the relative reactivities of the two substrates by comparing the relative conversions of each substrate. From these data, the k_X/k_H ratio was calculated and a graph of log(k_X/k_H) versus σ composed (Figure 2). Remarkably, a minimum centered at the origin is

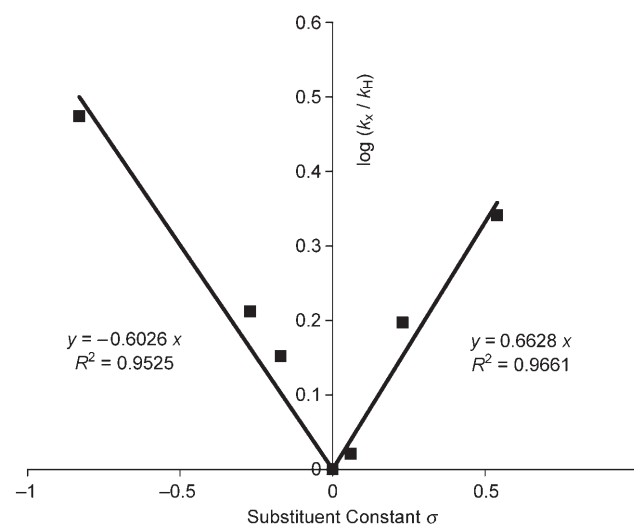
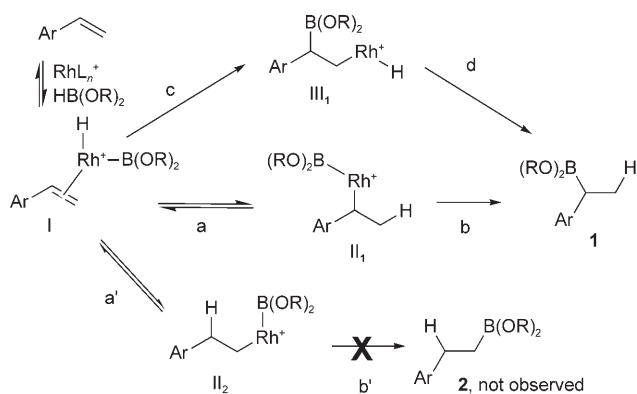


Figure 2. Hammett plot for styrene derivatives.

also observed, indicating a break in the mechanism for these substrates as well. A simple interpretation of these results would be that both the rate and the regioselectivity of the reaction are determined at the same point in the multi-step reaction and that both are influenced by the ability of aryl substituents to dissipate charge.

Unlike uncatalyzed hydroborations, the presence of a metal catalyst induces the sequential addition of boron and hydrogen across the olefin.^[1,28] The precise mechanism by which this occurs was the subject of considerable debate in the 1990s.^[30–33] Potential mechanisms include initial hydride transfer followed by reductive carbon–boron bond formation, boryl transfer followed by reductive elimination of hydrogen and sigma-bond metathesis.^[34]

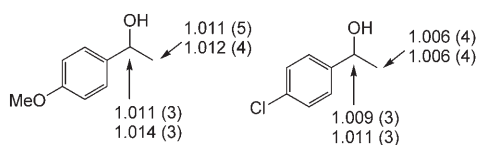
Theoretical work by Ziegler et al. provides support for both hydride and boryl insertion^[35] mechanisms and the feasibility of boryl insertion under mild conditions is demonstrated by the elegant diboration studies of Morken,^[36] Baker,^[37] Marder,^[37c] Westcott,^[38] and Fernandez and Peris.^[39] These two potential catalytic pathways are depicted in Scheme 1.^[40]



Scheme 1. Potential reaction pathways.^[40]

In order to obtain more information on the nature of the product-forming step in our system, a ^{13}C KIE study was carried out using the natural abundance method as described by Singelton.^[41] This technique provides information about the first irreversible step of the catalytic cycle.^[41] The KIE study was performed for *p*-methoxystyrene and *p*-chlorostyrene in order to provide mechanistic information for the two different pathways. Since the hydroboration reaction is accompanied by a trace of hydrogenation (ca. 2.5%) which would complicate recovery of the starting material, we chose to carry out the KIE studies by examination of the product at low conversion.

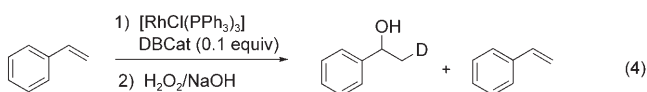
Approximately equal KIEs are observed at the benzylic and methyl carbons of *p*-methoxy phenethanol. In the case of the *p*-chloro derivative, the KIE observed at the methyl position is approximately half that observed at the methyl in the *p*-methoxy product (Scheme 2), but unfortunately the



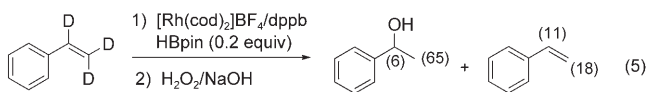
Scheme 2. Results of KIE studies.

small magnitude of the KIEs obtained and the errors that accompany the method complicates the comparison of these numbers. In the absence of additional data,^[42] a more detailed mechanistic analysis is not possible.

Thus we turned to deuterium labeling as a method to assess at least the first step of the reaction. It has been previously shown by Evans and Fu that with deuterated catechol borane, the combination of metal hydride(deuteride) addition and olefin decomplexation is irreversible.^[32,33] Deuterium is incorporated cleanly into the methyl group of the product, and when the reaction is run with an excess of alkene, no deuterium is incorporated into the recovered alkene [Eq. (4)].^[43]



A completely different picture emerges from the reaction of HBPIn with deuterated vinyl arenes or DBPin with protic substrates [Equation (5)], the numbers in parentheses indicate



the total observable label at each site based on initially added HBPIn]. The “H” from HBPIn is transferred mainly to the terminal position of the product but some label is observed at the benzylic position as well. In addition, recovered starting material is observed to have incorporated 29% of the label. Since 5 equivalents of the vinyl arene are employed, this implies that the hydride addition is reversible, although the forward reaction occurs on a similar time scale. These results demonstrate the dramatic mechanistic differences that can be observed when changing from catechol to pinacol borane. In this case, the reversibility and selectivity of the metal hydride addition is significantly different when the two ostensibly similar boranes are employed. This may signify a completely different mechanism, or at least a change in the rate-(turnover)-limiting step with a change in borane.

In conclusion, the reactions of vinyl arenes with pinacol borane catalyzed by cationic Rh species proceed through different mechanisms depending on the electronic properties of the arene. This is based on the observation of breaks in the respective Hammett plots for both intramolecular systems (unsymmetrical stilbenes) and intermolecular competitions between styrene and vinyl arenes. In concert with these results, deuterium labeling studies indicate that the mechanism of the hydroboration of olefins with HBPIn is significantly different from that observed with HBCat. The reasons for these differences and the elucidation of the two mechanisms at play in the hydroboration of olefins with HBPIn are the subject of current investigations.

Experimental Section

Hydroboration of *cis*-stilbenes 6a–g: The reaction was set up inside a glove box. To a sealed tube were added $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (10.15 mg, 5 mol %) and dppb (10.7 mg, 5 mol %). This mixture was dissolved in THF (4 mL) and stirred for 5 min. To the stirring suspension was successively added *cis*-4-fluorostilbene (99.1 mg, 0.50 mmol) and pinacolborane (87 μL , 0.60 mmol). The reaction tube was sealed within the glove box and removed to a fume hood. Reaction mixtures were then heated in an oil bath set at 80 °C for 3 days. The reaction flask was cooled to ambient temperature and 30% H_2O_2 (2 mL) and 2 M NaOH (2 mL) were added. The reaction was stirred vigorously for 2 h. The mixture was then subjected to an aqueous work-up procedure and extracted with ether. The crude product obtained from the ether phase was loaded onto a small biotage loading cartridge and chromatographed using a gradient elution 1–20% EtOAc in hexanes. ^1H NMR spectra were used to determine the isomer ratio by comparison with authentic samples of 7a–g prepared independently.

Styrene competition experiments: In a glove box, a round-bottomed flask was charged with $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (10.15 mg, 5 mol %) and dppb (10.7 mg, 5 mol %) in THF (2 mL). After stirring for 5 min, styrene (0.50 mmol) and *para*-substituted styrene (0.50 mmol) were

added simultaneously in THF (2 mL). Lastly pinacolborane (15 μ L, 0.10 mmol) was added. The reaction mixture was stirred in the glove box for 24 h. Upon removal of the flask from the glove box, the reaction was immediately quenched with aqueous ether. 80 μ L decane was added as GC internal standard. The relative conversion of each substrate was determined by GC. Results described in Table 1 are the averages of two runs.

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