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Electronic effects in asymmetric hydroboration

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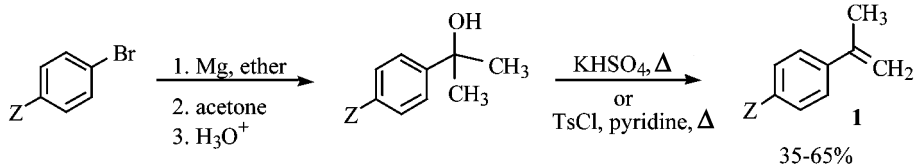
Abstract—To determine whether electronic effects are operative in asymmetric hydroboration, a series of *para*-substituted 2-aryl-1-propenes were prepared and reacted with four asymmetric borane reagents. A significant correlation between the electronic nature of the *para*-substituent and the degree of asymmetric induction was observed only for a chloroborane–ether complex, not for any of several simple alkylboranes. A quantitative analysis of the relative reactivities is also given.

The chemoselectivity, regioselectivity and stereospecificity of hydroboration has made it one of the more useful reactions in organic synthesis.[1] Asymmetric variants of this reaction have made a variety of compounds, especially secondary alcohols, available in high enantiomeric purity.[2] The effect of structural variations in the alkene on reactivity,[3] regiochemistry[4] and (for asymmetric hydroboration) asymmetric induction have been well studied.[2] Likewise, electronic effects on both reactivity[5] and regiochemistry[6] have been studied. However, there appears to have been no systematic study of how purely electronic effects influence the degree of asymmetric induction observed.[7] Indeed, the assumption seems to have been that in all enantioselective reactions steric factors are paramount, and electronic effects have rarely been studied.[8] A study of asymmetric hydroboration of a series of heterocyclic alkenes has been reported,[9] but this necessarily involved changing both sterics and electronics simultaneously.

To fully separate any steric effects from electronic effects, we undertook a classical Hammett study of the asymmetric hydroboration of a series of *para*-substituted 2-arylpropenes (**1**). These were generally prepared via a Grignard reaction as shown in Scheme 1.

For the asymmetric hydroboration reactions, we chose the three most widely-used chiral boranes: diisopinocampheylborane (IPC_2BH, **2**),[10] mono-isopinocamphylborane ($IPCBH_2$, **3**),[11] and dilongifolylborane (Lgf_2BH, **4**)[12] (Scheme 2). In addition, we also employed the readily-available but less well-known crystalline chloroborane complex **5**.[13] To analyze the optical purities of the products, we found that direct analytical separation of the 2-aryl-1-propanol enantiomers (**6**) was possible using a chiral GC separation (discussed later).

The asymmetric hydroboration of the 1-arylpropenes (**1**) with the chiral boranes were carried out at constant temperature (30°C) in either THF or (for chloroborane **5**) benzene, with the exception of $(IPC)_2BH$ which was carried out at 0°C in THF (Scheme 3). All the asymmetric hydroboration reactions were carried out at least



Scheme 1.

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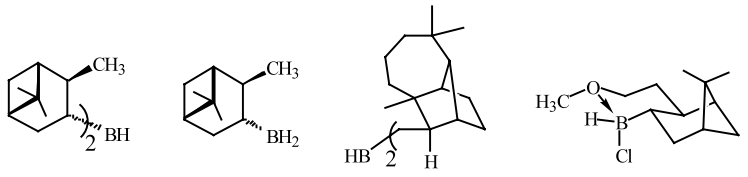
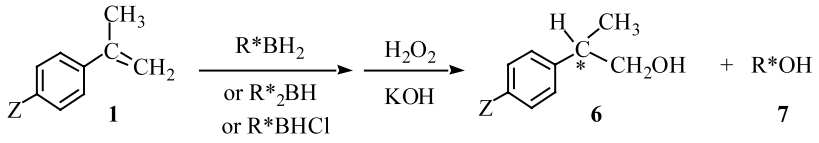


Ipc_2BH **2** $IpcBH_2$ **3** Lgf_2BH **4** **5**

Scheme 2.



Z = CF_3, Cl, F, H, CH_3, CH_3O, $N(CH_3)_2$

Scheme 3.

twice, and the reactions with chloroborane carried out in pairwise combinations with an internal standard which allowed determination of the relative rates[18] by GC analysis after oxidation. Oxidation with H_2O_2 and alcoholic[14] KOH cleanly gave 2-aryl-1-propanols (**6**) as well as the oxidized residue (**7**) of the borane reagent. The presence of 2-aryl-2-propanols was not detected by GC. In no case were we able to observe the alcohol from the dimethylamino-substituted alkene; it is possible that coordination between the amino group and the borane rendered the latter unreactive under these conditions. Probably because the chiral center is one carbon removed from the OH group, standard methods of optical purity analysis (e.g. chiral shift NMR or conversion to diastereomeric derivatives followed by NMR or GC analysis) gave ambiguous results with respect to the enantiomer ratio and/or the absolute configuration of the major product. However, chiral GC analysis using a Cyclosil-B column[15] was successful, giving adequate separation between enantiomers (resolution = 0.65–1.2), with the (*R*) enantiomer eluting first. In all cases, the alcohol residue from the chiral borane reagent was longer retained than any of the 2-aryl-1-propanols on the GC and did not interfere. The GC analysis was repeated three times on each sample; the run-to-run standard deviation on the % ee was generally less than 1% ee. The results are given in Table 1; negative values indicate that the (*R*) enantiomer predominated.

The presence of electronic effects were evaluated by the linearity and slope of a Hammett plot between log (enantiomer ratio) (which is proportional to $\Delta G^{\neq}$, the difference in activation energies leading to each enantiomer) and sigma-*para*.[16] None of the three simple alkylboranes studied (mono- and di-isopinocamphylborane, and dilongifolylborane) showed a significant electronic effect; in all these cases there was significant scatter ($r^2 = 0.01$–0.3) and the slope of the least-squares line was very shallow (0.01–0.15). However, in the case of chloroborane **5** there was a significant electronic effect observed (see Fig. 1), the least-squares line correlating well ($r^2 = 0.95$) and a significant slope was observed (−0.48). The electron-rich alkenes gave distinctly higher levels of asymmetric induction than electron poor alkenes.

We had anticipated that the electron-poor alkenes (i.e. Z = electron-withdrawing) would react the most slowly but give the 'tightest' transition state (i.e. closest approach between the borane and the alkene) and thus give the highest asymmetric induction. This would be consistent with the general principle of higher reactivity/lower selectivity that is often observed in a variety of reactions, and this behavior has been observed in the diastereoselective metal-catalyzed hydroboration of allylic alcohol derivatives.[7] However, we observe exactly the opposite with chloroborane **5**: the *p*-chloro

Table 1. Enantiomeric excesses observed in the asymmetric hydroboration/oxidation of a series of *p*-substituted 1-arylpropenes **1**. Positive values indicate that the (*S*) enantiomer predominated

Z group (sigma)[16]	$(IPC)_2BH$	$IPCBH_2$	$(Lgf)_2BH$	Chloroborane **5**	Relative rate with chloroborane **5**
CF_3 (0.53)	14	13	17	−5.6	0.15
Cl (0.24)	13	9	10	4	0.29
F (0.15)	9	−4	13	16	0.58
H (0.0)	3	−8	19	26	1
CH_3 (−0.14)	11	−0.5	16	26	2.2
OCH_3 (−0.12)	17	7	18	30	3.8

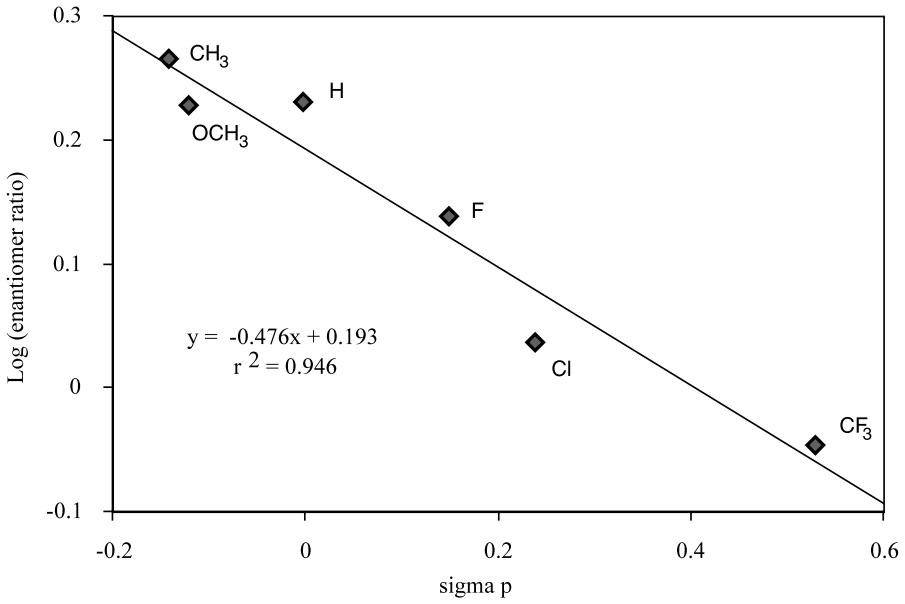


Figure 1. Hammett plot for asymmetric hydroboration of *para*-substituted α-methylstyrenes with chloroborane **5**.

alkene ($\sigma = 0.24$) gave nearly racemic product (0.5% ee), while the *p*-methyl compound ($\sigma = -0.14$)[16] gave 30% ee. Based on relative retention times and a previous study of α-methylstyrene,[17] the major enantiomer in all cases (except for CF_3) is of the (*S*) configuration. An interesting observation is that the strongest electron-withdrawing group (i.e. CF_3, $\sigma = 0.53$) gives the opposite enantiomer (*R*) as the major product. To our knowledge, there have been no reports of a change in the sense of asymmetric induction based on electronic effects alone. However, studies of electronic effects in asymmetric epoxidation reactions have also shown the degree of asymmetric induction to correlate with increasing electron donating character.[8] The hydroboration reactions of **5** were carried out pairwise, and we were able to determine the relative reactivities of the various alkenes using the Ingold–Shaw equation.[18] The relative reactivity (last column in Table 1) correlates well with sigma-*p* (see Fig. 2), and as expected,[5] alkenes containing the more electron-withdrawing groups are less reactive.

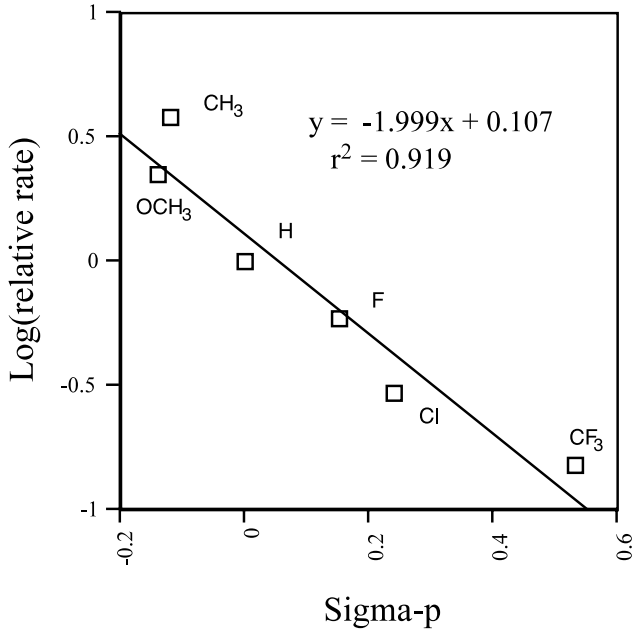


Figure 2. Plot of relative reactivity of chloroborane **5** with each *para*-substituted α-methylstyrene versus sigma-*p*.

This study establishes for the first time the operation of purely electronic effects in asymmetric hydroboration, as well as revealing an interesting dependence on borane electronics (i.e. chloroborane–ether complex versus simple alkylboranes) which may be of value in the design of new asymmetric reagents. Whether these electronic effects in chloroborane **5** are observed because of the presence of the chlorine or because of the internal coordination remains to be determined.

Acknowledgements

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