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Heterofunctional control of regio- and enantioselectivity in rhodium-catalysed hydroboration of allylic systems

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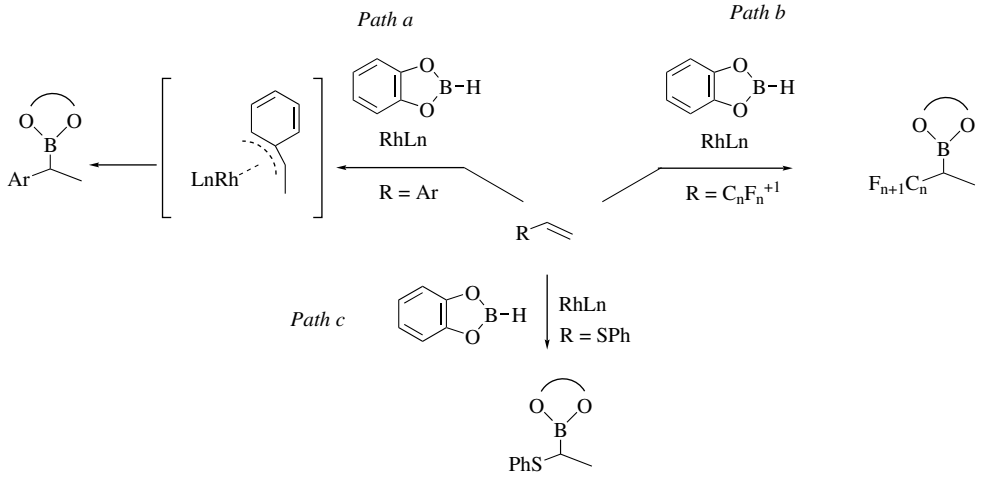
Abstract—Aryl allylic sulfones were reacted with catecholborane (HBcat) in the presence of neutral and cationic Rh complexes modified with bidentate chiral ligands, to produce the branched heteroorganoboronate ester, as the main isomer with moderate enantioselectivity. The relative rate of the formation of the secondary regioisomer seems to be sensitive to the nature of the catalytic system and the electronic effects of the substrate.

1. Introduction

The unusual secondary alcohol produced in the rhodium-catalysed hydroboration/oxidation of vinylarenes is believed to arise from metal-stabilisation of the benzylic intermediate during the catalytic cycle (Scheme 1, path a).[1,2] Either catalysed[3] or uncatalysed[4] hydroboration/oxidation reactions can also exhibit special control towards formation of the branched alcohol on perfluoroalkenes substrates, probably due to the combined electronic effects of the borane reagent and the substrate (Scheme 1, path b). Even more remarkable is the regiocontrol provided by the electronic properties of heteroatom-containing substrates,[5] such as phenyl vinyl sulfide, which regioselectively adds the boron unit from catecholborane at the 2-position of the alkene, in the rhodium-catalysed hydroboration reaction (Scheme 1, path c).[6]

However, the directing effects, which revealed a trend in regioisomeric branched organoborane formation, seem to diminish substantially from vinylic to allylic systems.



Scheme 1.

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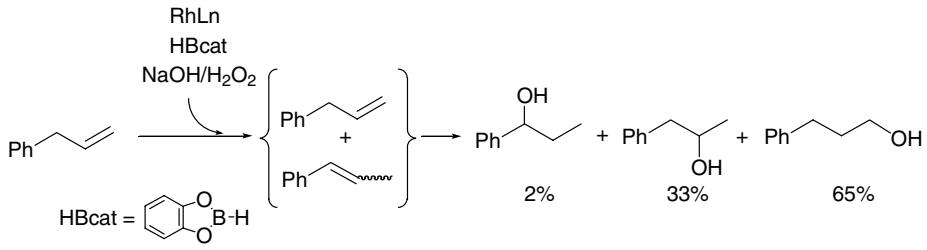
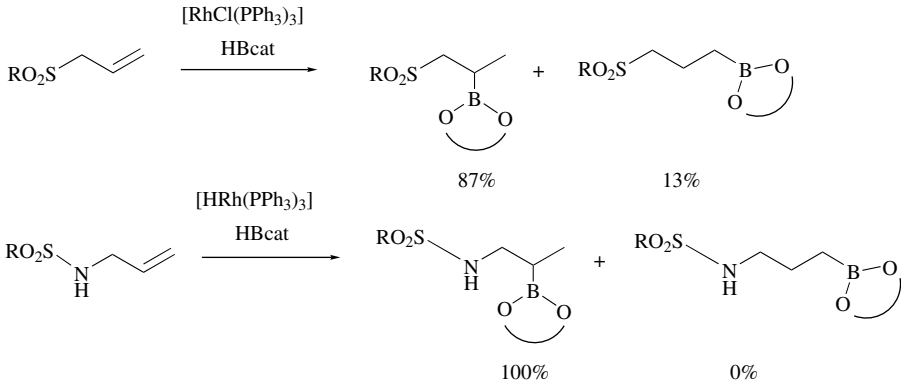


Scheme 2.



Scheme 3.

Such is the case for the hydroboration/oxidation of 1-phenylprop-2-ene,[7] which provided mixtures of primary and secondary regioisomers (Scheme 2). In addition this substrate, where the aromatic group is in β-position to the alkene moiety, can undergo isomerisation of the double bond, which favours the formation of 1-arylpropanol.

Surprisingly, the metal-catalysed hydroboration of some heteroatom substituted allylic substrates has furnished the desired branched heteroorganoboronate ester as a consequence of the nature of the catalyst. Thus, Wilkinson's catalyst precursor [$RhCl(PPh_3)_3$] favours the formation of the secondary boronate ester in the hydroboration of allyl sulfones[8] (Scheme 3), while [$HRh(PPh_3)_4$] does the same for the hydroboration of allyl sulfonamides[9] (Scheme 3).

The reversed regioselectivity from terminal B–H addition in aliphatic and unfunctionalised terminal alkenes to the branched manner in vinylic systems made it possible to study an asymmetric version of the catalysed hydroboration/oxidation of vinylarenes[10] and more recently, we explored the case of perfluoroalkenes.[11] However, to the best of our knowledge no work has been carried out in this respect for heteroatom-containing allylic substrates.

In this context and as a result of our ongoing research into the use of organoboranes for the synthesis of enantiomerically pure organic compounds, we herein report a direct and simple method for generating enantiomerically enriched heterofunctionalised alcohols. Due to the synthetic utility of chiral organosulfurboronate esters in biological applications,[12] we decided to examine the catalytic chiral hydroboration/oxidation of allyl sulfones, to determine whether it was possible to preferentially obtain one of the enantiomers of 1-(phenylsulfonyl)-2-propanol.

2. Results and discussion

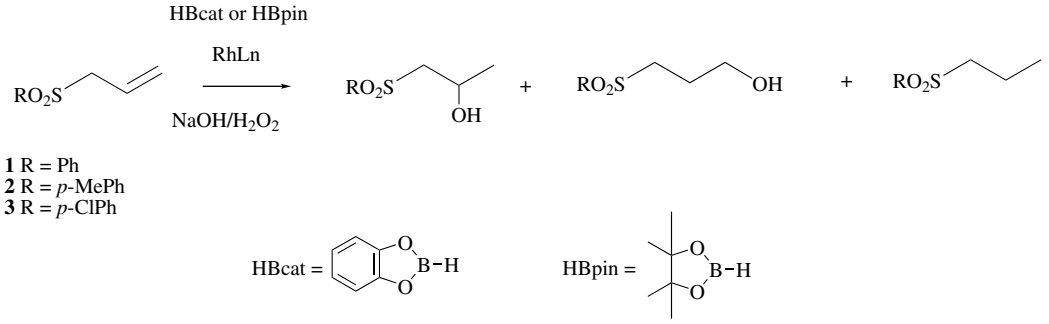
Hou and Dai's observations on the catalytic hydroboration of allyl sulfones[8] show that the neutral Rh(I) precursor of catalyst [$RhCl(PPh_3)_3$] favours addition of the catecholboryl unit at the 2-position of the terminal alkene. When we re-examined this reactivity, we first found that the conversion of the substrate was total and that, as well as the branched and linear hydroborated/oxidated products, small percentages of hydrogenated derivatives could be obtained as a consequence of the partial formation of the metal complex $RhH_2Cl(PPh_3)_3$[13] (Table 1, entries 1 and 2; Scheme 4).

In the hydroboration/oxidation of phenyl allyl sulfones, an excess of hydroborating reagent seemed to be necessary to guarantee a high selectivity (Table 1, entry 3). A low chemo- and regioselection towards the branched alcohol was detected when the sterically hindered hydroborating reagent pinacolborane was used instead of catecholborane (Table 1, entry 4). Next, we decided to study how Rh-neutral and Rh-cationic catalytic systems affected the activity and selectivity of hydroboration of organosulfur substituted 1-alkenes. Like Wilkinson's

Table 1. Rhodium-catalysed hydroboration/oxidation of phenyl allyl sulfone, **1**[a]

Entry	Catalytic system	Conversion (%)[b]	PhO_2S OH (%)[b]	PhO_2S OH (%)[b]	PhO_2S (%)[b]
1[c]	$[RhCl(PPh_3)_3]$	83	87	13	—
2	$[RhCl(PPh_3)_3]$	100	86.2	8.2	5.6
3[d]	$[RhCl(PPh_3)_3]$	100	37	43	20
4[e]	$[RhCl(PPh_3)_3]$	100	42.3	18	39.7
5	$[Rh(\mu\text{-}Cl)(COD)]_2$ + 6equiv PPh_3	100	84.2	10.1	5.7
6	$[Rh(\mu\text{-}Cl)(NBD)]_2$ + 6equiv PPh_3	100	84.3	9.7	6
7	$[Rh(COD)_2]BF_4$ + 2equiv PPh_3	100	54	32.8	13.2
8[f]	$[Rh(COD)_2]BF_4$ + 2equiv PPh_3	100	94	—	6

[a] Standard conditions: substrate/hydroborating reagent HBcat/Rh = 1/3/0.0075; solvent: THF; T: 25 °C; t: 4 h.
[b] Conversion and selectivity calculated by ^1H NMR.
[c] Ref. 9, where 3 mol % of Rh catalyst is used.
[d] Hbcat (1 equiv).
[e] Hydroborating reagent: Hbpin (3 equiv).
[f] Addition of 3 equiv of $BnMe_3NCl$.



Scheme 4.

catalyst precursor, a preferentially secondary insertion of the alkene into the metal complex formed from $[Rh(\mu\text{-}Cl)(COD)]_2$/6 equiv PPh_3 $[Rh(\mu\text{-}Cl)(NBD)]_2$/6 equiv PPh_3 has was observed (Table 1, entries 5 and 6). These results differ from the preferential primary insertion of organofluoro substituted 1-alkenes with neutral catalytic systems.[3]

As a general behaviour, the catalytic hydroboration of phenyl allyl sulfones with neutral Rh complexes provides higher selectivity towards branched organosulfurboronate esters than cationic Rh complexes (Table 1, entry 7). The considerable neutralising influence of chlorine as counterion was confirmed in a new experiment in which the salt $BnMe_3NCl$ was added to the catalytic system formed from $[Rh(COD)_2]BF_4/PPh_3$ (Table 1, entry 8) because the products were distributed in a very similar way to when the system $[Rh(\mu\text{-}Cl)(COD)]_2$/6 equiv PPh_3 was used.

Taking into account all these preliminary experiments, we envisaged that chiral bidentate phosphine ligands might lead to the desired branched boronate ester with some asymmetric induction. The ligands considered for this study were those described in Figure 1, which form five-, six- and seven-membered rings on chelation with rhodium.

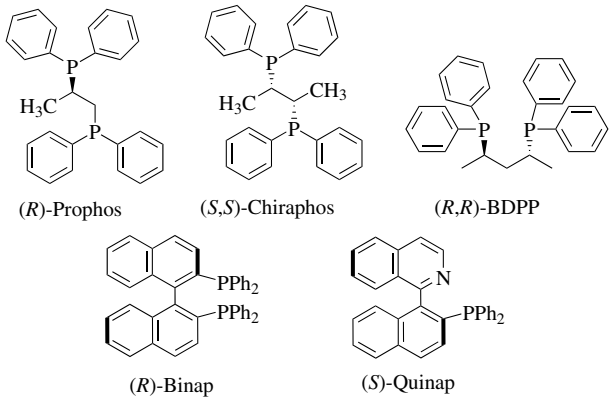


Figure 1.

To analyse to what extent the relative activity, regio- and enantioselectivity are sensitive functions of the chiral ligand, new catalytic hydroboration/oxidation reactions of phenyl allyl sulfone were performed with cationic and neutral Rh complexes modified with (*R*)-Prophos, (*S*,*S*)-Chiraphos, (*R*,*R*)-BDPP, (*R*)-Binap and (*S*)-Quinap. Conversion of the substrate was complete after 4 h but selectivity for the secondary alcohol was significantly dependent on the nature of the Rh

Table 2. Catalytic asymmetric hydroboration/oxidation of phenyl allyl sulfone with Rh complexes and HBcat[a]

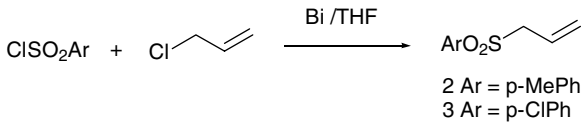
Entry	Catalytic system	Conv. (%)[b]	Secondary alcohol (%)[b]	ee (%)[c]
1	$[Rh(COD)_2]BF_4$ + (*R*)-Prophos	100	90	8 (*S*)
2	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*R*)-Prophos	100	54	3 (*S*)
3	$[Rh(COD)_2]BF_4$ + (*S*,*S*)-Chiraphos	100	88	17 (*S*)
4	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*S*,*S*)-Chiraphos	100	69	11 (*S*)
5	$[Rh(COD)_2]BF_4$ + (*R*,*R*)-BDPP	100	98	30 (*S*)
6	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*R*,*R*)-BDPP	100	77	33 (*S*)
7	$[Rh(COD)_2]BF_4$ + (*R*)-Binap	100	74	22 (*S*)
8[d]	$[Rh(COD)_2]BF_4$ + (*R*)-Binap	100	12	39 (*S*)
9	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*R*)-Binap	100	87	38 (*S*)
10[e]	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*R*)-Binap	100	87	38 (*S*)
11	$[Rh(COD)_2]BF_4$ + (*S*)-Quinap	100	85	12 (*R*)
12	$[Rh(\mu\text{-Cl})(COD)]_2$ + (*S*)-Quinap	100	89	12 (*R*)

[a] Standard conditions: substrate/catecholborane/Rh = 1/3/0.0075; solvent = THF; $T = 25$ °C; $t = 4$ h.
[b] Conversion and selectivity calculated by ^{1}H NMR.
[c] Enantiomeric excess determined by GC with a chiral column, as derivative alcohols. Absolute configuration by comparison with Ref. 15.
[d] Hydroborating reagent HBpin.
[e] $T = -20$ °C.

complex and the chiral ligand. Small percentages of hydrogenated product could be observed. For those ligands, which chelate with rhodium to form five- and six-membered rings, (*R*)-Prophos, (*S*,*S*)-Chiraphos, (*R*,*R*)-BDPP, major regioselection was observed for the secondary alcohol with the cationic rhodium catalytic system (Table 2, entries 1–6). A certain level of enantioenrichment (ee = 30–33.4%) was attained when ligand (*R*,*R*)-BDPP was involved (Table 2, entries 5 and 6). However, when the atropoisomeric chiral ligand (*R*)-Binap chelates with rhodium to form a seven-membered ring, a change in the dependency of the electronic nature of the metal complex was detected. Major regioselectivity towards the secondary alcohol was associated with the neutral rhodium catalytic systems, which were also responsible for the highest ee values obtained in this preliminary study (Table 2, entries 7–10). The use of other hydroborating reagents or lower reaction temperatures did not improve these results. In an attempt to combine the beneficial effects of the atropoisomeric ligand (*R*)-Binap and the ability to chelate with rhodium and form a six-membered ring by (*R*,*R*)-BDPP, we next focused on the atropoisomeric heterotopic chiral ligand (*S*)-Quinap, which chelates with Rh to form a six-membered ring. However, despite the efficiency shown by this P,N ligand in several enantioselective syntheses,[14] we were disappointed to observe that while regioselectivity remained high, enantioselectivity decreased significatively.

At this point, we can infer two things from our initial asymmetric catalytic results. Firstly, regioselectivity for the secondary alcohol depends upon the electronic properties of the substrate, but also on the electronic properties of the metal complex used as the catalyst. To highlight the importance of this point, we carried out two catalytic reactions with the analogue neutral complex $[Ir(\mu\text{-Cl})(COD)]_2$ modified with (*R*)-Binap and (*S*)-Quinap. However, only 23% and 28% of the secondary alcohol was observed, respectively, with almost no ee's values. Secondly, enantioselectivity seemed to be favoured with chiral ligands that form major chelate rings with rhodium(I) complexes.

We demonstrated the generality of the regio- and enantioselective hydroboration/oxidation reaction of aryl allyl sulfones as a function of the electronic and steric properties, by carrying out the catalytic reaction on electron-rich and electron-deficient substituted phenyl allyl sulfones. Of the many sulfone synthetic procedures described in the literature,[16] we prepared the *p*-methylphenyl allyl sulfone, **2**, and *p*-chlorophenyl allyl sulfone, **3**, with an efficient and inexpensive protocol, which uses the bismuth-catalysed coupling of allylic halides with the corresponding sulfonyl chloride, under mild conditions[17] (Scheme 5).



Scheme 5.

The results of the Rh-catalysed hydroboration/oxidation of **2** and **3** were similar to the phenyl allyl sulfone. The data are summarised in Table 3. Almost complete regioselectivity for the secondary alcohol was achieved when $[Rh(COD)_2]BF_4$/(*R*,*R*)-BDPP was used as a catalyst precursor (Table 3, entries 1 and 7) and ee values around 33% were determined from the ^{1}H NMR spectrum in the presence of the chiral shift reagent $Eu(TFC)_3$. Contrary to the strong electronic influence of the aryl sulfonyl functional group on the branched isomer formation, additional beneficial effect by aryl substitution with electron-withdrawing groups was detected. The asymmetric induction has not either been affected by any aryl substitution on the aryl allyl sulfone.

Table 3. Catalytic asymmetric hydroboration/oxidation of substituted phenyl allyl sulfone with Rh complexes and HBcat[a]

Entry	Catalytic system	Substrate	Secondary alcohol (%)[b]	ee (%)[c]
1	$[Rh(COD)_2]BF_4 + (R,R)$-BDPP	2	98	34 (*S*)
2	$[Rh(\mu\text{-Cl})(COD)]_2 + (R,R)$-BDPP	2	49	33 (*S*)
3	$[Rh(COD)_2]BF_4 + (R)$-Binap	2	74	11 (*S*)
4	$[Rh(\mu\text{-Cl})(COD)]_2 + (R)$-Binap	2	52	7 (*S*)
5	$[Rh(COD)_2]BF_4 + (S)$-Quinap	2	70	16 (*R*)
6	$[Rh(\mu\text{-Cl})(COD)]_2 + (S)$-Quinap	2	76	25 (*R*)
7	$[Rh(COD)_2]BF_4 + (R,R)$-BDPP	3	95	33 (*S*)
8	$[Rh(\mu\text{-Cl})(COD)]_2 + (R,R)$-BDPP	3	37	30 (*S*)
9	$[Rh(COD)_2]BF_4 + (R)$-Binap	3	73	17 (*S*)
10	$[Rh(\mu\text{-Cl})(COD)]_2 + (R)$-Binap	3	38	13 (*S*)
11	$[Rh(COD)_2]BF_4 + (S)$-Quinap	3	50	7 (*R*)
12	$[Rh(\mu\text{-Cl})(COD)]_2 + (S)$-Quinap	3	38	16 (*R*)

[a] Standard conditions: substrate/catecholborane/Rh = 1/3/0.0075; solvent = THF; $T = 25$ °C; $t = 4$ h.
[b] Conversion (100% in all cases) and selectivity calculated by ^{1}H NMR.
[c] Enantiomeric excess determined by ^{1}H NMR in the presence of chiral shift reagent Eu(TFC)$_3$. Absolute configuration by comparison with Ref. 15.

3. Conclusion

We can conclude that we have performed the first example of direct access to enantiomerically enriched mixtures of 1-phenylsulfonyl-2-propanol, by varying the catalytic system throughout the hydroboration/oxidation of aryl allyl sulfones with catecholborane. Given the importance of sulfur-substituted 2-propanols as sulfur-containing chiral synthons in asymmetric organic synthesis,[18] we believe these results provide an unexplored synthetic alternative, via organoborane chemistry, that deserves further study in the near future.

Acknowledgements

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