Regiochemical control of the catalytic asymmetric hydroboration of 1,2-diarylalkenes

Antonia Black, John M. Brown* and Christophe Pichon†

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The hydroboration of stilbenes and related disubstituted alkenes catalysed by QUINAP complexes may proceed with high enantio- and regioselectivity; rhodium and iridium catalysts give the same product regioisomer but opposite enantiomers.

The Rh-complex catalysed asymmetric hydroboration of styrenes with secondary boronate esters may proceed with high enantioselectivity, affording a route to benzylic alcohols,[1,2] primary or secondary amines,[3] or carboxylic acids.[4] Chelating phosphinamine ligands have shown broader substrate scope than diphosphines and can be effective at ambient temperature. The 2,2′-disubstituted biaryl P–N moiety introduced with QUINAP,[5] has been modified and more recently extended in this context.[6] Although catecholborane is most widely used as reagent, good results have been obtained recently with pinacolborane.[7] There is a general, albeit ligand-dependent,[8] favouring of boron delivery to the benzylic position of a vinylarene. This follows a pattern established for many related Rh-catalysed X–H additions, including hydrosilylation and hydroformylation.[9] The Spencer–Yu test demonstrates preferential Rh addition to the benzyl position of β-substituted styrenes in hydrogenation.[10]

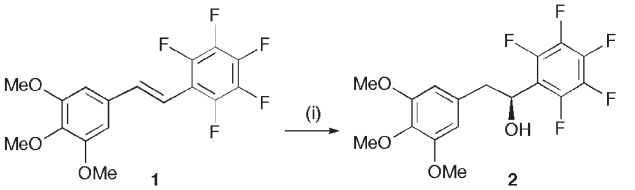
The Rh-complex catalysed hydroboration/oxidation of (*E*)- or (*Z*)-stilbene can be carried out in good e.e. using QUINAP as ligand.[11] We have been interested in the factors controlling regiochemistry when the stilbene is unsymmetrical, for synthetic and mechanistic reasons. The alkene **1** was prepared and reacted with catecholborane under the conditions of Scheme 1, with conventional oxidation of the intermediate boronate; the alcohol product was analysed. Only one regioisomer **2** was detected, as confirmed from the three-bond C*H*$_2$ *o*-Ar*H* coupling observed in the HMBC spectrum. This was shown to be the (*S*)-enantiomer‡ formed in 77% isolated yield and 88% e.e. by comparison of the CD spectrum in EtOH with an authentic sample of (*S*)-1,2-diphenylethanol prepared by asymmetric hydroboration, of known absolute configuration.[12] A similar level of enantioselectivity had previously been found for either isomer of the parent alkene stilbene, and compares with e.e. ranges of 53–87 (*E*), and 59–99 (*Z*) obtained with the related quinazoline-based ligand family developed by Guiry and co-workers, the only other examples of asymmetric stilbene hydroboration reported to occur in high e.e.[6a] The same direction of catecholborane addition was observed in its thermal reaction to alkene **1**, which occurred with 95% regioselectivity. When the corresponding dppb complex was employed as catalyst, the alternative regioisomer was obtained preferentially albeit with weak selectivity (Scheme 1).

These initial results encouraged the hydroboration of a range of unsymmetrical (*E*)-stilbenes, designed to probe steric and especially electronic effects. Results are outlined in Table 1.§

Not only is the QUINAPRh$^+$ hydroboration far more regioselective than the corresponding hydroboration with dppbRh$^+$, but its direction is predictable. The secondary alcohol arising from C–B oxidation is preferentially formed adjacent to the more electron-deficient of the two arenes in the QUINAPRh$^+$ case. A weaker but similar trend in the dppbRh$^+$ reactions is overridden by the steric effect of *o*-F substituents; *cf.* the first and last entries of Table 1. As in previous studies, the e.e. is highest when the arene is electron-rich, and much diminished by the presence of strongly electron-withdrawing groups other than fluorine. This is illustrated by the results obtained with simple styrenes bearing the same substituents, shown in Scheme 2.

An interesting example of the interplay between electronic and steric effects is afforded by the substituted 1,1-diphenylethylene **10**. This gives predominantly the tertiary alcohol **11** with QUINAPRh$^+$, albeit in low enantiomer excess, whilst the primary alcohol **12** is clearly preferred in the case of dppbRh$^+$. This further illustrates the sensitivity of the diphosphine catalyst to steric effects (Scheme 3).

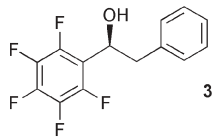
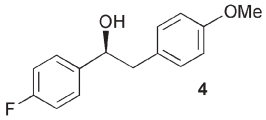
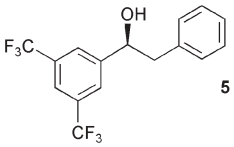
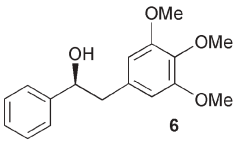
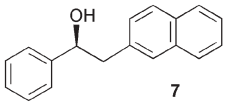
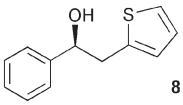
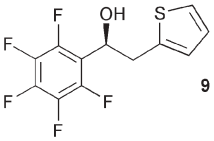
The regiochemical control observed in these reactions encouraged a reexamination of the claim that asymmetric hydroboration with rhodium catalysts proceeds by a different mechanism from hydroboration with iridium catalysts.[14] Iridium catalysts are known to reverse the stereochemical course, and to account for this it was suggested that C–B formation precedes C–H formation.



Scheme 1 (i) Catecholborane (1 equiv.), (**1**) (1 equiv.), 2 mol% QUINAPRh$^+$OTf$^-$, RT, 16 h, then 1 mol% catalyst, catecholborane (0.5 equiv.), 16 h, RT; for Dppb$^+$OTf$^-$, 2 mol% catalyst, 16 h; thermally – catecholborane (4 equiv.), 70 °C, 5 h. Oxidative workup was with 30% aq. H_2O_2 in 1 M NaOH.

Chemical Research Laboratory, Mansfield Rd., Oxford, UK OX1 3TA. E-mail: john.brown@chem.ox.ac.uk; Fax: 44 1865 285002; Tel: 44 1865 275642
† *Present address*: LECSO-UMR 7582, Université Paris XII, 2 rue Henri-Dunant, 94320 Thiais, France.

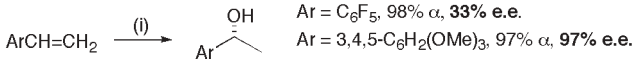
Table 1 Hydroboration of unsymmetrical stilbenes with QUINAPRh$^+$

Reactant $Ar_1CH{=}CHAr_2$	Major Product	Yield *E.e.*[a]	Regioselectivity[b]
Ar_1 = Ph Ar_2 = C_6F_5	 **3**	**55** *60*	**100 (20)**
Ar_1 = *p*-MeOPh Ar_2 = *p*-FPh	 **4**	**51** *83*	**83**
Ar_1 = Ph Ar_2 = 3,5-$(CF_3)_2$Ph	 **5**	**49** *29*	**90**
Ar_1 = Ph Ar_2 = 3,4,5-$(MeO)_3$Ph	 **6**	**48** *85*	**90 (60)**
Ar_1 = Ph Ar_2 = 2-naphthyl[c]	 **7**	**62** *67*	**80 (63)**
Ar_1 = Ph Ar_2 = 2-thiophenyl	 **8**	**72** *95*	**75 (60)**
Ar_1 = C_6F_5 Ar_2 = 2-thiophenyl[d]	 **9**	**81** *83*	**100 (45)**

[a] E.e.'s were determined by HPLC (Diacel OD, C_6H_{12}/i-PrOH), or by the P(III) method.[13] [b] Bracketed values refer to the selectivity towards the same regioisomer employing dppbRh$^+$. [c] (*Z*)-Isomer of alkene. [d] See text for discussion of the reaction with QUINAPIr$^+PF_6^-$ which gives the opposite hand of product **9**.

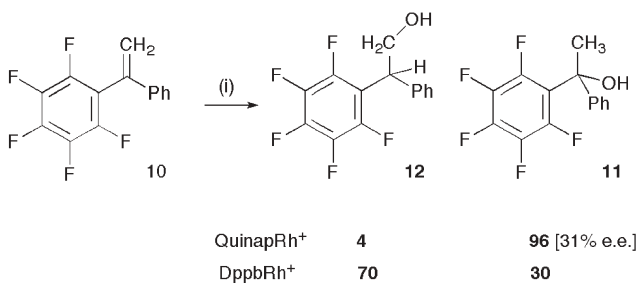
This possibility is effectively ruled out by the direct comparison between QUINAPRh$^+$ and QUINAPIr$^+$ as catalysts for the asymmetric hydroboration, both leading to the same regioisomer **9**, (the last entry of Table 1). Both the reactivity (40% yield) and enantioselectivity are lower in the iridium case and the configuration of the product is reversed, an e.e. of 33% (*R*) being observed.

Success in the regiochemical control of stilbene hydroborations encouraged us to examine the differentially protected *bis*-catechol derivative **13**, prepared by intramolecular Heck reaction *via* vinylarene **14** (from piperonal) and bromide **15**. Asymmetric hydroboration using QUINAPRh$^+$ proceeded with pleasingly high regioselectivity and enantioselectivity, such that a single product was readily isolated from the reaction at 0 °C in ⩾ 98% regioselectivity (Scheme 4). The structure **16** was that expected from the precedents of boron transfer to the more electron-deficient carbon of the alkene. The observed specificity demonstrates clearly just how sensitive is the hydroboration step to electronic effects.

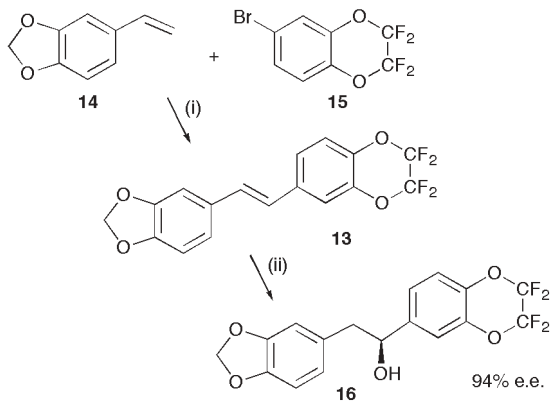


Scheme 2 Conditions as Scheme 1(i), yields 69%; 91%.

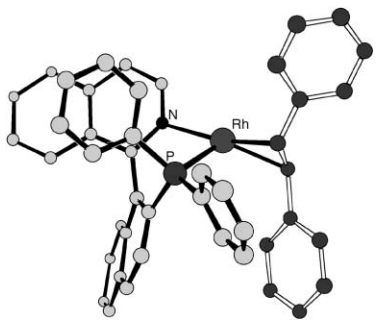
The high levels of regiochemical control observed, especially in the QUINAPRh$^+$ case, indicate that the catalyst can actively function to enhance selectivity. Good enantioselectivity can be obtained adjacent to an electron-withdrawing arene in the stilbene but not the styrene case (compare Schemes 1 and 2). In other asymmetric catalytic reactions arene–arene interactions have been convincingly proposed to explain observed specificities.[15] In the present case analysis is facilitated by the availability of X-ray structures for (*E*)-stilbene diphosphine complexes.[16] Model building based on derived parameters, and existing QUINAPPd



Scheme 3 (i) Conditions as Scheme 1(i); 66% yield in QUINAPRh hydroboration.



Scheme 4 (i) $PdCl_2/P(o\text{-tolyl})_3$, (2 mol%), **14** (1.25 equiv.), **15** (1 equiv.), Et_3N, 100 °C, 85%; (ii) conditions as Scheme 1(i), 0 °C, 78%.



Scheme 5 Stilbene *si*-face coordination in asymmetric hydroboration using (*S*)-QUINAPRh$^+$ based on the N-*trans*-alkene model. H atoms are omitted for clarity.

structures,[17] is informative. When the stilbene is η^2-coordinated *trans*- to N with (*S*)-ligand,[18] only *si*-face coordination is sterically permissible (Scheme 5). This may also lead to favourable face–face π-stacking between the electron-rich naphthyl and the more electron-deficient aryl ring of the alkene.

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Notes and references

‡ The configuration of products **2**, **3** and **8** was (*S*), by CD; all exhibited a positive Cotton effect in the 215–250 nm range.

§ Typical procedure: Freshly prepared *rac*-(COD)RhQUINAP (32 mg, 0.04 mmol, 2 mol%) was dissolved in THF (2 ml) under an argon atmosphere. 1,2,3,4,5-Pentafluoro-6-[(*E*)-2-(3,4,5-trimethoxyphenyl)-vinyl]-benzene (0.720 g, 2 mmol) was dissolved in THF (0.5 ml) and added to the catalyst, together with freshly distilled catecholborane (220 μl, 2 mmol) and stirred. After 16 h Rh(COD)(±)QUINAP (16 mg, 0.02 mmol) and catecholborane (110 μl, 1 mmol) were added to the reaction and stirred for a further 16 h to yield a brown solution. Analysis of the brown oil by ^{11}B and ^1H NMR, after concentration, showed a single regioisomer. The reaction was quenched with ethanol (4 ml) and cooled to 0 °C prior to the addition of H_2O_2 (30% aq, 4 ml) and NaOH (2 M in H_2O, 5 ml). The reaction was allowed to warm to room temperature and stirred for 16 h until golden yellow. The reaction was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic phases were washed with NaOH (1 M in H_2O, 40 ml), water (2 × 20 ml) and brine (30 ml), dried ($MgSO_4$), filtered through silica to remove the catalyst and the solvent removed *in vacuo* to yield the single isomer 1-pentafluorophenyl-2-(3,4,5-trimethoxyphenyl)ethanol as analytically pure white crystals (529 mg, 70%), mp = 135–137 °C. δ_H (400 MHz; $CDCl_3$) 6.41 (2H, s, Ar-H), 5.30 (1H, dd, C*H*OH, J = 5.8, 8.4 Hz), 3.87 (6H, s, *m*-CH_3 × 2), 3.86 (3H, s, *p*-CH_3), 3.26 (1H, dd, CH_2CHOH, J = 5.8, 14.1 Hz), 3.03 (1H, dd, CH_2CHOH, J = 8.4, 14.1 Hz), 2.00 (1H, bs, OH); δ_C (100.6 MHz; $CDCl_3$) 153.3, 137.1, 132.0 (Ar-C), 106.0 (Ar-CH), 67.0 (*C*HOH), 60.7 (*p*-CH_3), 56.0 (*m*-CH_3 × 2), 43.2 (*C*H_2CHOH); δ_F (376.5 MHz; $CDCl_3$) −142.90 (*p*), −154.54 (*o*), −161.59 (*m*); ν_{max}/cm^{-1} (Nujol), 3419 (br, s, OH), 2725 (m, OMe), 1460 (s, C=CH), 1128 (s, C–F), 721 (w, C–F); λ_{max} (CH_2Cl_2) 227 (log ε 3.1), 265 (log ε 2.3); HRMS (M^+) calculated for $C_{17}H_{16}F_5O_4$: 379.0947; found 379.0956. Repetition with enantiomerically pure (*S*)-catalyst gave 1-pentafluorophenyl-2-(3,4,5-trimethoxyphenyl)ethanol (537 mg, 71%); 88% (*S*) by HPLC (227 nm, cyclohexane : IPA/98 : 2, 1 ml/min, rt = 19.6 and 23.1); $[\alpha]_D^{22}$ 18.5 (c = 0.2, CH_2Cl_2).

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