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Catalytic Asymmetric Hydroboration with Oxazaborolidines

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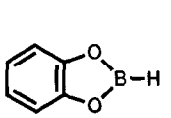
Summary: The cyclic secondary boranes derived from ephedrine and pseudoephedrine undergo rhodium complex-catalysed hydroboration of styrenes; both the regiochemistry and derived enantiomeric excess depend strongly on the structure of the catalyst with the ferrocenebiphosphine complex (**12d**) the most promising to date.

Since the original observation of rhodium-catalysed olefin hydroboration reactions by Mannig and Noth[1], there has been extensive development of the basic reaction. In their early work, $ClRh(PPh_3)_3$ was found to be the most effective among many organometallic catalysts examined but only catecholborane (**1**) and 2,2,4-trimethyldioxaborinane (2) were activated towards olefins; other secondary heterocyclic boranes including (3) were not subject to catalytic activation . Evans and coworkers developed the synthetic applicability of catalytic hydroboration by demonstrating diastereoselectivity in addition to allylic alcohols and their silyl derivatives[2], and Burgess showed that the asymmetric hydroboration of a variety of prochiral olefins catalysed by rhodium complexes of BINAP or DIOP occurred in up to 76% e.e., although temperatures of -25°C or lower were generally required for high enantioselectivity[3]. Further advances were made by Hayashi, who demonstrated that the hydroboration of styrene proceeded with very high e.e. when catalysed by rhodium BINAP complexes at low temperatures[4]. The reaction occurred with high regioselectivity to the secondary borane, and hence to the secondary alcohol by oxidation. Related results have been obtained by these and other workers in the field[5] and the beginning of a mechanistic rationale has been proposed[6]. In all of this work, the hydroborating agent was catecholborane, following the original precedent.



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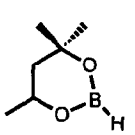

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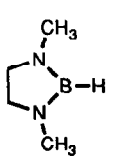

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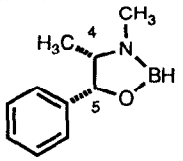
Since the chemistry of hydroboration owes much of its synthetic power to the variation in control and reactivity afforded by substitution at boron, it is surprising that no further developments in the structure of the borane have been reported for the catalysed reaction. We show that homochiral oxazaborolidines, simply derived from the inexpensive chiral auxiliaries ephedrine and pseudoephedrine, are very effective in the Rh-catalysed hydroboration reaction and show substantial promise in asymmetric synthesis.

The reagent (4S,5R)-ephedrineborane (**4**) ($[\alpha]_D^{20}$= -108 (c=1, $CHCl_3$); δ ($CDCl_3$) 5.58, 3.68 ; $J_{4,5}$ = 8.5 Hz) was prepared as previously described[7] and isolated by short-path distillation (bp 45^{0}C (bath), 0.1mmHg.). In similar manner, the (4S,5S) diastereomer (**5**) was prepared from pseudoephedrine($[\alpha]_D^{20}$= +59 (c=1, $CHCl_3$); δ 4.90, 3.30; $J_{4,5}$ = 7.0 Hz). Reaction proceeds in two stages, first the formation of an O-borate with displacement of one mole of H_2 at room temperature and then the elimination of a second mole of H_2 which requires heating to 120^{0}C. In the pseudoephedrine case this first intermediate (**6**) was isolated. A further observation in this case was that the initially formed oxazaborolidine oligomerised to a crystalline material, m.p. 99-102^{0}C, ($[\alpha]_D^{20}$= -125 (c=1, $CHCl_3$)(R,R-isomer); δ($CDCl_3$) 4.66, 2.70 ; $J_{4,5}$ = 9.6 Hz); the structure of this compound (**5**)$_n$ is under active investigation.



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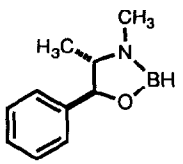

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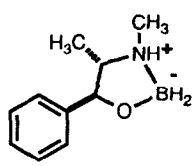

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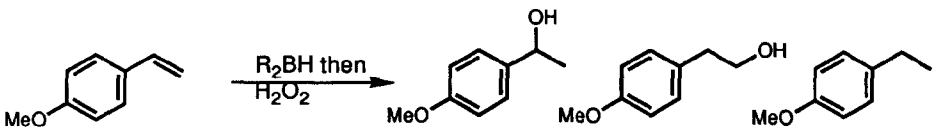
Initial experiments were carried out with 4-methoxystyrene (**7**), which reacted with borane (**5**) only very sluggishly at 100^{0}C and gave >90% 2-arylethanol (**9**) after oxidation of the reaction product with alkaline H_2O_2. In the presence of 1 mol% of either $ClRh(PPh_3)_3$ or $HRh(PPh_3)_4$ in thf then reaction proceeds smoothly at ambient temperature. After oxidative workup a mixture of 1-arylethanol (**8**), primary alcohol (**9**) and ethylbenzene (**10**) was formed in which the secondary alcohol was the main component, although both regioselectivity and chemoselectivity were modest. The optical purity of the chiral alcohol (**8**) was determined by reaction with (S)- O-acetylmandelic acid (CH_2Cl_2, 4-DMAP, DCC)[8]. The two diastereomeric O-Me groups in (**11**) gave distinct ^{1}H NMR resonances (δ(C_5D_5N) 3.59 (S,S) ; 3.62 (S,R)) permitting simple estimation of the optical yield (Table 1). The significant value of 17(S) obtained with borane (**4**) clearly demonstrates the intimate involvement of the ephedrine moiety in the catalytic step leading to stereoselection, and encouraged further study. The course of reaction was altered little by lowering the reaction temperature but improved by changing the solvent to glyme. With the pseudoephedrine-derived borane (**5**) the yield of secondary alcohol formed by catalytic hydroboration / oxidation was significantly higher and of greater enantiomeric purity (56(R)).

Some initial efforts have been made to improve the reaction selectivity by variation of the catalyst using both chiral and achiral biphosphines, and the results obtained are highly dependent on the structure of the ligand. Cationic rhodium bicyclo[2,2,1]heptadiene trifluoromethanesulphonates were prepared by the method previously described[9]. With the flexible chelate (**12a**) as catalyst both boranes added to 4-methoxystyrene with high regioselectivity in a rapid process, but one essentially devoid of enantioselectivity. The flexible chiral biphosphine (**12b**) also gives reasonable regioselectivity towards the secondary isomer, and although the products from ephedrineborane (**4**) are of low enantioselectivity they are of opposite hand for the RR and SS-enantiomers of (**12b**), demonstrating that both ligand and borane play a part in determining the optical yield. This double asymmetric induction is very evident when the catalyst (**12c**) is derived from R- or S-BINAP.



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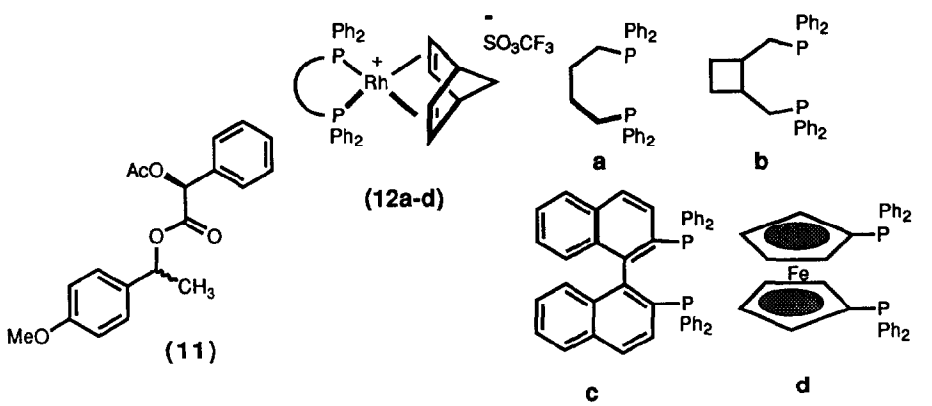
Borane	Catalyst	(8)	E.e.	(9)	(10)
(4)	PPh_3/Rh	36	17(S)	28	36
(4)*	PPh_3/Rh	63	31(S)	25	12
(4)	(12a)	95	5(S)	5	0
(4)	(12b)(R)	84	15(S)	10	6
(4)	(12b)(S)	75	31(R)	13	12
(4)	(12c)(R)	32	86(S)	37	31
(4)	(12c)(S)	25	8(S)	38	38
(5)	PPh_3/Rh	53	55(R)	24	23
(5)*	PPh_3/Rh	58	56(R)	24	18
(5)	(12a)	96	6(S)	2	2
(5)	(12c)(R)	low		low	major
(5)	(12c)(S)	42	83(R)	28	30
(5)**	**(12d)**	**82**	**76(S)**	**14**	**4**
(6)	PPh_3/Rh	0		0	100
$(5)_n$**	(12d)	low	low	low	major

Table 1. Hydroboration reactions. Typical conditions: 1 mol% Rh catalyst, 0.4 mmol olefin,0.56 mmols borane, 0.6 ml thf, 20°C,1-12 h.. Values of (8),(9) and (10) quoted as ratios/100. The d.e. of borane adduct from (5) by NMR is equal to the e.e. of derived alcohol estimated after oxidation. (*) in glyme. (**)(4R,5R) -isomer.



For (4S,5R) ephedrineborane (**4**) the reaction proceeds slowly in high e.e. but modest regioselectivity using R-BINAP. The reaction is accompanied by a substantial amount of hydrogenation, as is often seen with slow catalytic hydroborations. With S-BINAP derived catalyst, the regioselectivity is rather worse and the e.e insignificant. Likewise for the pseudoephedrineborane (**5**) the two hands of BINAP give substantially different results (Table 1) but in some runs hydrogenation was the dominant pathway. Although e.e. values close to 90% are observed the utility is limited by poor regiochemical control. The preferred enantiomer is opposite to that obtained with catecholborane and Rh-(S)-BINAP catalysts[4]; we have verified that at room temperature in thf hydroboration of 4-methoxystyrene proceeds with 68% e.e.(S), and 80% regioselectivity. This reversal of stereochemical course suggests interesting mechanistic complexities. The most promising results to date have been obtained with complex (**12d**) and borane (4R,5R)-(**5**). Here a rapid catalytic reaction ensues at 0^0C or above in which the chemoselectivity is 82% for formation of the secondary borane and the S-enantiomer of 1-arylethanol is produced after oxidation in 76% e.e. With the dimeric borane $(5)_n$ however, the reaction proceeds very slowly and mainly to hydrogenation. The success of this combination of (**5**) and (**12d**) may relate in part to the large bite angle[10] (97^0) and moderate rigidity of the biphosphinerhodium complex.

Hydrogenation is a side-reaction in many cases, as has been observed elsewhere[2]. Attempts to carry out hydroboration using complex (**6**) led to hydrogenation with complete exclusion of competing reaction pathways. This transfer hydrogenation pathway was also operative for α-ethylstyrene, albeit accompanied by isomerisation. These preliminary results, verified in some cases with the parent styrene, demonstrate the potential of oxazaborolidines derived from readily available chiral amino-alcohols in asymmetric hydroboration. Both the borane and the catalyst play a part in determining the configuration and optical efficiency of the product. Future work will concentrate on the optimisation of regio- and enantioselectivity, and the mechanism of catalytic asymmetric hydroboration with oxazaborolidines.

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