Chapter 1

Introduction and scope

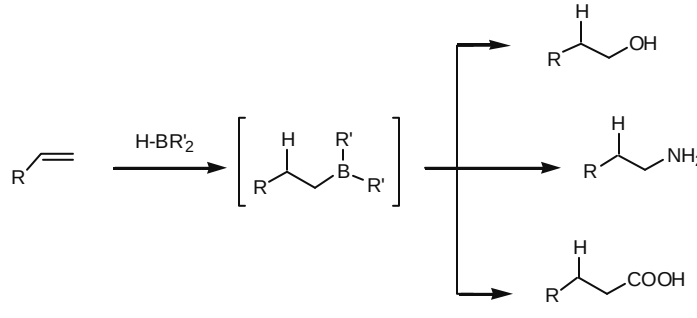
The catalytic asymmetric hydroboration reaction has proved to be one of the most useful reactions in organic synthesis. It provides a way of transforming alkenes into many different types of C-X and C*-R bonds through the optically enriched organoboron adduct C*-B. In addition, there are a wide range of unsaturated substrates, which can react with a borane reagent through transition metal complexes.*

There are several challenges involved in applying chiral catalysts in the hydroboration reaction: the catalytic performance must be excellent, the development of the activity and selectivity during the process must be understood and chiral catalytic systems must be designed so that they can be recovered and reused, and, in this way, ensure the environmental and economic viability of the process. Taking these factors into account, we considered various hypotheses for our work. At that time, the academic challenges for this thesis were being defined and outlined in a paper but, as in any study of a chemical transformation, there is a hierarchy of goals to be met, the first of which was to know the state of the art.

Therefore, this section attempts to provide the reader with a general overview of the principal concepts and applications of the homogeneous catalytic hydroboration reaction, as well as the leading approaches involved in the recycling of soluble catalysts through immobilisation pathways.

1. Hydroboration reaction

The hydroboration reaction is a classical method for synthesising organoboron compounds and one of the most studied reactions in organic synthesis. Introduced by H. C. Brown [1] in 1959, it is based on the *syn* addition of borane reagent H-BR'$_2$ to alkenes or alkynes. In fact, it is considered to be the initial step in the introduction of a very wide variety of functional groups and it can also be used to construct carbon frameworks (Scheme 1). The uncatalysed hydroboration reaction is one of the most common and useful methodologies for large-scale preparations, but metal-catalysed reactions are more efficient and selective. However, catalysed hydroboration did not start to show significant results until Männing and Nörth's developments in 1985 [2]. They reported that the addition of the borane reagent, catecholborane (**1**), to alkenes is generally very slow at room temperature but that it can be considerably accelerated by small amounts of transition-metal complexes, such as Wilkinson's complex [RhCl(PPh$_3$)$_3$]. In addition, catalysed hydroboration is an interesting strategy for highlighting the chemo-, regio-, diastereo-, and enantioselectivity of the process. This opened up a completely new field of chemistry, which prompted intensive investigation [3].



Scheme 1

The different products of the catalysed and uncatalysed [4] reactions reflect different mechanisms for the hydroboration transformation. Moreover, the asymmetric

version of the hydroboration reaction can be performed by using catalysts containing chiral ligands and/or chiral borane reagents [5].

Organoboron compounds have been shown to be of practical help in synthetic organic reactions, such as asymmetric, combinatorial and polymer synthesis [3], [6-8], molecular recognition such as host-guest compounds [9], and neutron capture therapy in the treatment of malignant melanomas and brain tumours [10].

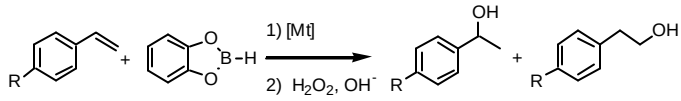
2. Metal-catalysed hydroboration

The first significant difference between the uncatalysed and catalysed hydroboration reaction is the reaction conditions. The B-H addition to unsaturated functional groups in the absence of catalyst requires elevated temperatures and long reaction times. In contrast, the hydroboration reaction catalysed by transition metal complexes can not only be carried out at room temperature [3a] but can also provide different chemo- [11], regio- and stereoselectivities in the process. The hydroboration reaction of unsaturated substrates catalysed by transition metal complexes has been intensively studied, particularly from the point of view of its mechanism. In this introduction we only consider the most general mechanistic features because any specific mechanism will depend on the nature of the substrate, the catalyst, the reagent and the conditions.

2.1. Hydroboration of alkenes and alkynes

Unsaturated vinylarenes, aliphatic terminal alkenes, perfluoroalkenes, alkynes, conjugate dienes, allenes and enynes have been shown by the literature to be suitable substrates for the catalytic hydroboration reaction. The hydroboration of vinylarenes has been extensively studied, and perhaps these are the best substrates that a discussion of the efficiency and selectivity of the catalyst should consider. The following review aims to provide an overall picture of the catalysed hydroboration of unsaturated substrates, particularly vinylarenes (Table 1).

Table 1. Catalytic systems for hydroboration/oxidation of vinylarenes with catecholborane[a]



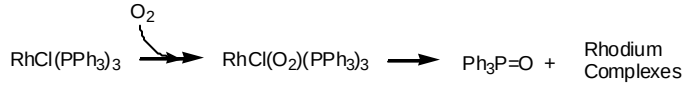
1 **2** **3**

Entry	Catalytic system	Yield (%)	**2** (%)	**3** (%)
1	$RhCl(PPh_3)_3$	80	>99	<1
2[b]	$RhCl(PPh_3)_3$		24	76
3	$[Rh(\mu\text{-}Cl)I(cod)]_2$	45	20	80
4	$[Rh(\mu\text{-}Cl)(cod)]_2/4PPh_3$	90	98	2
5	$[Rh(\mu\text{-}Cl)(cod)]_2$/2dppe	50	34	66
6	$[Rh(\mu\text{-}Cl)(cod)]_2$/2dppb	83	45	55
7	$[Rh(\mu\text{-}Cl)(cod)]_2$/2dppf	83	10	90
8	$[Rh(\eta^3\text{-}2\text{-Me-allyl})(dppb)]$		>99	<1
9	$[Rh(BABAR\text{-}Phos)_4]CF_3SO_3$	99	99	1
10	$[Rh(cod)_2]BF_4/2PPh_3$	93	99	1
11	$[Rh(cod)_2]BF_4$/dppb	94	99	1
12	$[Ir(cod)(Py)(PCy_3)]OTf$		22	78
13	$RuCl_2(PPh_3)_4$		-	100
14	$RuCl_2(PPh_3)_4(MeOH)$		1	99
15[c]	Cp_2TiMe_2	89	-	100
16[c]	$Cp^*_2Sm(THF)$	89	-	100

[a] Standard conditions. Solvent: THF. T: 25^{0}C, under argon; [b] under air;
[c] Standard conditions. Solvent: benzene. T: 25^{0}C, under argon

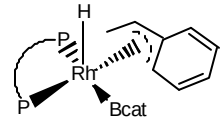
Neutral rhodium-phosphine complexes, such as Wilkinson's catalyst, $[RhCl(PPh_3)_3]$, are the catalysts that have been most studied for the hydroboration of alkenes. However, the sensitivity of the metal complex to air and, therefore, its undesired influence on the regioselectivity of the hydroboration reaction have been described in the literature (Table 1, entries 1 and 2) [12-13]. The oxidation of the

phosphine to their corresponding oxide decreases the phosphine/rhodium ratio and, consequently, there are changes in regioselectivity [14], (Scheme 2). Thus, the *in situ* preparation of the catalyst from $[Rh(\mu\text{-}Cl)(cod)]_2$ and the phosphine (Table 1, entries 3-7) [12-15] or the use of an air-stable complex such as π-allylrhodium, $[Rh(\eta^3\text{-}2\text{-}Me\text{-}allyl)(dppb)]$ (Table 1, entry 8) [16] or the cationic complex $[Rh(BABAR\text{-}Phos)_4]CF_3SO_3$ (Table 1, entry 9) [17] are convenient alternatives. Also the *in situ* addition of monophosphines, (PPh_3), or diphosphines, (dppb), to the cationic rhodium complex $[Rh(cod)_2]BF_4$, generates highly active species that can catalyse the hydroboration reaction, even at low temperatures (Table 1, entries 10-11) [15].



Scheme 2

In the hydroboration of vinylarenes, the preference for branched (**2**) or linear (**3**) alkylboronate ester products (Table 1) depends on the catalytic system, the ligand and the borane reagent. Unfortunately, however, until now this has not been well understood. Hayashi et al. suggested that the high internal selectivity of the catalytic hydroboration of vinylarenes on the branched products could be favoured by a contribution from the η^3-benzylrhodium complex (**4**) (Figure 1) as a key intermediate [15a]. But in general, substrates such as perfluoroalkenes [18] and α,β-unsaturated esters or amides [19], which contain an electron-withdrawing group, commonly have high internal selectivities in the hydroboration reaction catalysed with cationic rhodium complexes and catecholborane (**1**).



4

Figure 1

Most studies of the catalysed hydroboration reaction have used the five-member ring heterocycle diorganyloxyborane catecholborane (**1**), (Figure 2), because of its high degree of Lewis acidity and the favourable steric profile of the borane coordinated to the metal [20]. However, during the hydroboration reaction the intrinsic instability of **1** favours side reactions, which lead to undesirable products such as alkanes or vinylboronate esters [21]. The pinacolborane (**5**), (Figure 2), has recently been found to be an excellent alternative as a borane reagent because it is more stable, easily stored and easily prepared [22]. Other borane reagents including 4,4,6-trimethyl-1,3,2-dioxaborilane (**6**) [23], oxazaborolidines (**7**) [24], benzo-1,3,2-diazaborolane (**8**) [25] and borazine (**9**) [26] might also be used, but the total scope of these reagents remains to be explored.

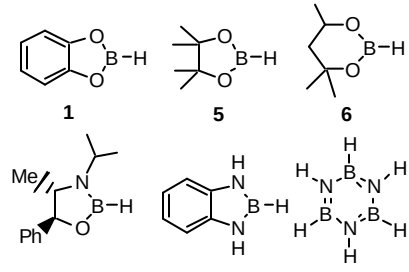
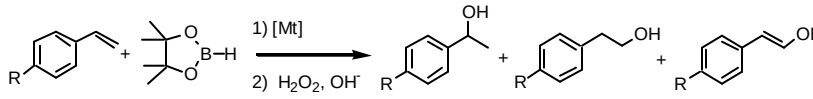


Figure 2

Several transition metals are used in the catalytic hydroboration/oxidation reaction with catecholborane as the borane reagent. Iridium (I) [27] and ruthenium (II) or (III) [28] are some of the transition metals that have been studied. Modified with phosphines, their selectivity towards terminal alcohols is high (Table 1, entries 12-14). However, the scope of these catalysts has not yet been studied in detail. The Ti and Sm metals modified with cyclopentadienyl ligands, Cp_2TiMe_2 [29] and $Cp^*_2SmMe_2$ [30] have proved to be excellent catalysts for the addition of boron to the terminal carbon of the substrate (Table 1, entries 15-16). Recently Lin et al., made a theoretical study of the mechanism in the hydroboration reaction of $Cp_2Ti(\eta^2\text{-HBcat})$ [31]. They suggested that there was a strong tendency to form a five-member ring

structural intermediate through the C-B interaction, which leads to the exclusive linear product. The steric effect of borane reagents also plays an important role in this selectivity. Throughout the literature, it can be observed that changes in the nature of the catalytic complex or in the hydroboration reagent have effects on the regioselectivity of the hydroboration reaction. When the catecholborane (**1**) is replaced by the pinacolborane (**5**) (Figure 2), the selectivity in the hydroboration reaction of vinylarene rhodium catalysts decreases. Thus, pinacolborane is added selectively to the terminal carbon of vinylarenes because of its bulkiness (Table 2, entries 1 and 2), which is in sharp contrast to the addition of catecholborane according to the electronic effect of the vinylarene. However, $RhCl(PPh_3)_3$ provides an undesired product, PhCH=CHOH (**10**), due to the 'dehydrogenative borylation' reaction (Table 2, entry 1). In addition, Ni(II), and Ir(I) catalysts reveal high terminal selectivity (Table 2, entries 3-4), [32-33].

Table 2. Catalytic systems for hydroboration/oxidation of vinylarenes with pinacolborane.



5 **2** **3** **10**

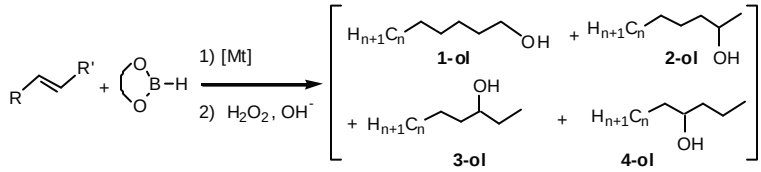
Entry	Catalytic system	Yield (%)	**2** (%)	**3** (%)	**10** (%)
1	$RhCl(PPh_3)_3$	99	35	50	15
2	$RhCO(PPh_3)_2Cl$	99	1	99	-
3	$CpNiCl(PPh_3)$	99	1	99	-
4	$[Ir(\mu\text{-}Cl)(cod)]_2$/2dppp	97	<1	>99	-

[a] Standard conditions. Solvent: CH_2Cl_2. T: 25^0C, under argon

It is worth mentioning that various metal complexes also catalyse the addition of catecholborane and pinacolborane to aliphatic terminal alkenes [2]. Neither the borane reagents nor the modified catalysts were able to change the high terminal regioselectivity (Table 3) also provided by the uncatalysed hydroboration

reaction with catecholborane (Table 3, entry 1) [13]. Similarly, the catalytic systems based on Rh, Zr, and Ir with pinacolborane show terminal regioselectivity (Table 3, entries 4-6) [32-35]. The terminal aliphatic alkene, 1-octene, and the internal alkene, 4-octene, can isomerise from internal or terminal alkenes to terminal or internal ones, respectively, in the presence of rhodium complexes and BH_3 as the borane reagent (Table 3, entries 3, 7) [13], [36]. In the case of internal alkenes, for example, the hydroboration/oxidation of 4-octene yields terminal or internal alcohols depending on the borane and catalyst used. The neutral rhodium and the cationic iridium complexes

Table 3. Catalytic hydroboration/oxidation of aliphatic alkenes. Isomerisation pathways[a]

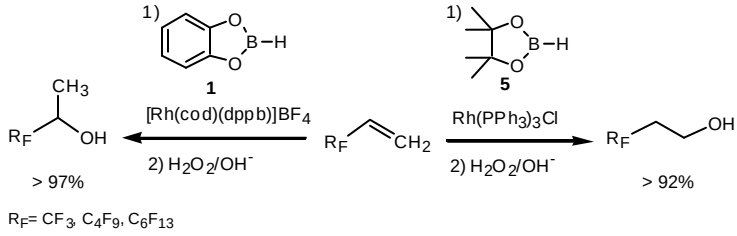


Entry	Catalytic system		Olefin	1-ol	2-ol	3-ol	4-ol
1	None	**1**	1-decene	98	2	-	-
2[b]	$RhCl(PPh_3)_3$	"	"	99	1	-	-
3[b]	$RhCl_3$	BH_3	1-octene	2	17	37	43
4	$RhCl(PPh_3)_3$	**5**	"	100	-	-	-
5	Cp_2ZrHCl	"	"	100	-	-	-
6	$[Ir(\mu\text{-}Cl)(cod)]_2$/2dppm	"	"	>99	<1	-	-
7[b]	$RhCl_3$	BH_3	4-octene	2	16	35	46
8	$RhCl(PPh_3)_3$	**5**	"	100	-	-	-
9	$[Ir(\mu\text{-}Cl)(cod)]_2$/2dppm	**5**	"	100	-	-	-
10[b]	$RhCl(PPh_3)_3$	**1**	"	-	-	-	100
11[b]	$[Rh(nbd)(dppb)]BF_4$	"	"	4	2	7	87
12	$[Rh(CO)(PPh_3)_2Cl]$	**5**	"	3	-	-	97
13	$Cp_2NiCl(PPh_3)_3$	"	"	1	-	-	99

[a] Standard conditions. Solvent: CH_2Cl_2. T: 25 ^{0}C, under argon; [b] Solvent: THF. T: 25 ^{0}C, under argon

are more prone to isomerise the boron atom to the terminal carbon in the presence of a bulky pinacolborane [32], [34]. This illustrates the superiority of pinacolborane for synthesising terminal boron compounds (Table 3, entries 8 and 9) [32-34]. However, catalytic systems based on rhodium and nickel provide mainly the 4-ol product regardless of whether the borane used is pinacolborane or catecholborane (Table 3, entries 10-13) [13], [32]. The alkene isomerization is caused by olefin insertion into the Rh-H bond, followed by β-hydride elimination, which seems to take place much more quickly than reductive elimination to give the C-B bond.

The regioselectivity of the hydroboration/oxidation of perfluoroalkenes ($R_FCH=CH_2$) is clearly reversed with regard to the borane reagent or the catalytic system used in the hydroboration reaction. P.V.Ramanchandran et al. [18] observed that branched perfluoroalkylboranate esters could be achieved by cationic rhodium complexes with unhindered boranes such as catecholborane. However, the same authors reported that linear perfluoroalkylboranate esters can also be easily prepared from neutral rhodium complexes with hindered boranes such as pinacolborane (Scheme 3).



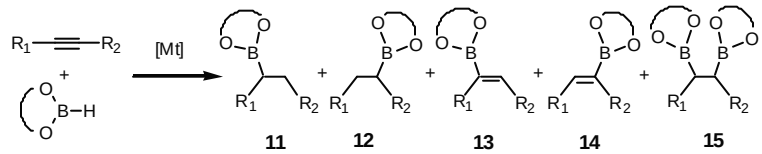
Scheme 3

On the other hand, whereas uncatalysed hydroboration of alkynes with dioxaborinanes requires either elevated temperatures or an excess of borane reagent [22-23], the catalysed hydroboration of alkynes with catecholborane or pinacolborane afforded (E)-1-alkenylboron compounds at room temperature. In fact, the transition metal-catalysed hydroboration of alkynes had not received much attention until Burgess and coworkers reported that the hydroboration of phenylacetylene with catecholborane catalysed by rhodium complexes gave a complex mixture of two

regioisomers of alkenylboronates (**13** and **14**), two hydrogenation products of **13** and **14** (**11** and **12**) and a diboration product **15** (Table 4, entry 1) [12].

The regioselectivity towards the terminal alkenylboronate isomer **14** is improved in the hydroboration/oxidation of phenylacetylene with $Cp_2Ti(CO)_2$ (Table 4, entry 3) [29] and nickel or palladium complexes modified with phosphine [37]. The regioselectivities obtained with rhodium [32], nickel [32] and zirconium [38] complexes with the borane reagent pinacolborane are similar (Table 4, entries 5-7). The results in Table 4 for hydroboration of phenylacethylene seem to show that the catalysed borane addition to terminal alkynes has no significant advantages over the uncatalysed reaction, as far as the regioselectivity is concerned. However, regiodifferentiation is greater between the catalysed and uncatalysed hydroboration of internal alkynes. For example, depending on the catalytic system, the regioselectivity can be reversed in the hydroboration of 1-phenyl-1-propyne (Table 4, entries 8 and 9).

Table 4. Catalytic hydroboration reaction of alkynes[a]



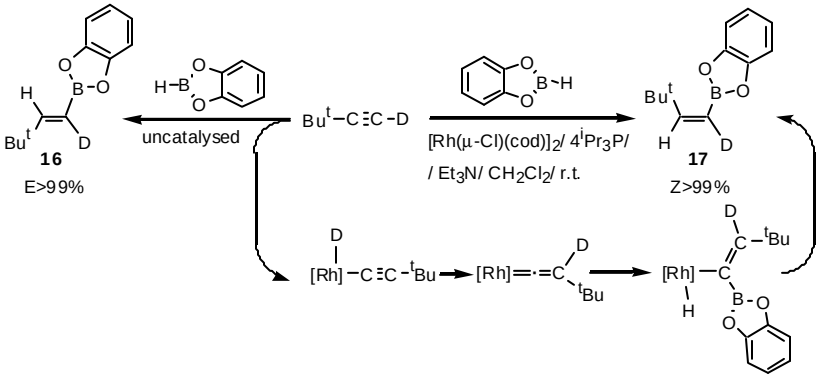
Entry	Catalytic system		R_1	R_2	Product distribution (%) **11**	**12**	**13**	**14**	**15**
1	$RhCl(PPh_3)_3/PPh_3$	**1**	Ph	H	29	9	16	17	29
2	$[Rh(\mu\text{-}Cl)(cod)]_2/8PPh_3$	"	"	"	54	19	-	-	27
3	$Cp_2Ti(CO)_2$	"	"	"	-	-	-	100	-
4	$RhCl(PPh_3)_3$	**5**	Ph	H	-	-	52	48	-
5	$[Rh(CO)(PPh_3)Cl]$	"	"	"	-	-	2	98	-
6	Cp_2ZrHCl	"	"	"	-	-	1	99	-
7	$CpNiCl(PPh_3)$	"	"	"	-	-	2	98	-
8	$Cp_2Ti(CO)_2$	**1**	Ph	Me	-	-	67	33	-

9	$NiCl_2$(dppe)	"	"	"	-	-	33	67	-

[a] Standard conditions. Solvent: THF, T: 25°C, under argon

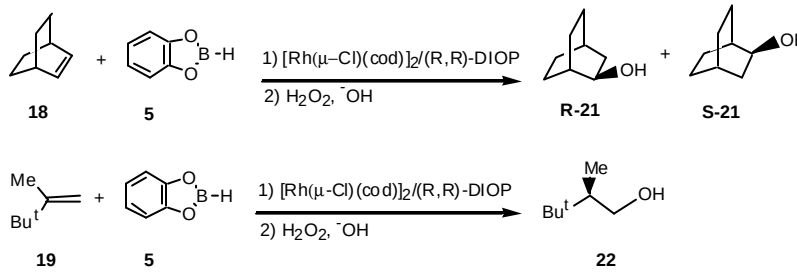
Whereas the $Cp_2Ti(CO)_2$ [32] favours the addition of boron to the carbon adjacent to the phenyl group because of electronic considerations, the steric hindrance of the phosphine ligand of $NiCl_2$(dppe) [39] forces the addition to the β-carbon.

Recently, Miyaura et al., [40], reported an interesting catalysed *trans*-hydroboration reaction for terminal alkynes, which directly provides the (Z)-1-alkenylboronate product. The uncatalysed route for obtaining the *cis*-1-alkenylboron compounds involves steps based on the intramolecular S_N2 substitution of 1-halo-1-alkenylboronates with metal hydrides [41-43] and the *cis*-hydrogenation of 1-alkynylboronates [44]. The hydroboration of 2-*tert*-butylethyne in the presence of the Rh(I)/P^iPr_3 and Ir(I)/P^iPr_3 catalytic systems with an excess of catecholborane or pinacolborane and one equivalent of triethylamine mainly provided the *cis*-1-alkenylboron compound **17** shown in scheme 4. The deuterated studies that they made showed that the presence of the amine should favour the oxidative addition of the C-D bond to the metal, rather than the oxidative addition of the borane reagent [45] (Scheme 4). Another example of contrasting ethynyl hydroboration pathways has recently been reported [46]. This study describes the synthesis of a novel tris-hydroboration product from the reaction of dimesitylborane with 2,5-diethynylpyridine.



Scheme 4

In 1988, the first catalytic asymmetric hydroboration of olefins was reported by Burgess et al. [47] for substrates such as norbornene (**18**) and 2-*tert*-butylpropene (**19**) in the presence of $[Rh(\mu\text{-}Cl)(cod)]_2$ with the chiral diphosphine (R,R)-Diop, (**20**) (Figure 3), as the catalyst (Scheme 5). Both substrates were transformed into the enantiomerically enriched mixture of the alcohols norbornol (**21**) (57% e.e in R) and 2,3,3-trimethylbutanol (**22**) (69% e.e in R) [47a] (Table 5, entries 1 and 2).



Scheme 5

Burgess and coworkers improved the enantiomeric excess in the hydroboration of norbornene using analogous reaction conditions but varying the bidentate chiral diphosphine ligand to (S,S)-BDPP (**23**) and 2-MeODiop (**24**) (Figure 3) (Table 5, entries 3 and 4) [47b].

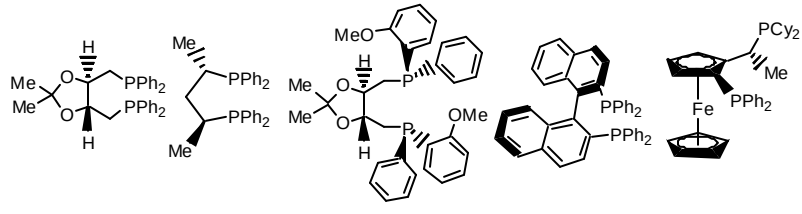
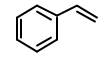


Figure 3

Table 5. Catalytic asymmetric hydroboration reaction of alkenes with Rh/(P,P) complexes[a]

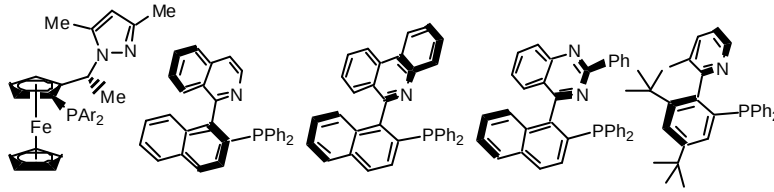
Entry	Ligand (P,P)	Substrate	T(^{0}C)	Yield (%)	e.e (%)[b]
1[e]	(R,R)-(-)-Diop (**20**)		-25	>99	57
2[e]	"		-25	>99	69
3[e]	(S,S)-BDPP(**23**)		-25	>95	80
4[c], [e]	2-(R,R)-MeODiop (**24**)	"	-25	>95	82
5[d]	(R)-(+)-Binap (**25**)		-30	90	70
6[d], [f]	"	"	-78	91	96
7[d], [g]	(S,R)-Josiphos (**26**)	"	-70	65	91.5

[a] Standard conditions. Solvent: THF, under argon; [b] Absolute Configuration R; [c] Solvent: Toluene; [d] Solvent: DME; [e] Rh cat.: $[Rh(\mu\text{-}Cl)(cod)]_2$; [f] Rh cat.: $[Rh(cod)_2]BF_4$; [g] Rh cat.: $[Rh(nbd)_2]BF_4$

The hydroboration of styrene catalysed by rhodium complexes modified with the atropoisomeric type chiral P,P ligand Binap (**25**) was found to proceed regioselectively in DME at low temperatures (-30ºC), followed by oxidation to give 1-phenylethanol with 70% enantiomeric excess (Table 5, entry 5) [15]. In addition, the enantioselectivity increased to 96% when the reaction was carried out at -78% (Table 5, entry 6).

Togni et al [48] obtained a similar enantiocontrol in the hydroboration oxidation of styrenes when they used rhodium complexes modified with ferrocenyldiphosphine, Josiphos (**26**), (Figure 3) (Table 5, entry 7) and the related pyrazole containing phosphinamine **27** ligand (Figure 4) (Table 6, entry 1). However, so far the best results have been obtained by Brown et al. in the catalytic hydroboration/oxidation reaction of vinylarenes using the effective chiral P,N-type ligand Quinap (**28**) (Figure 4) coordinated to rhodium complexes (Table 6, entries 2-

4). Substrates such as *p*-MeO-styrene were transformed into their corresponding α-alcohol with 94% e.e [49] at room temperature. The Quinap is less bulky than Binap in the region of the isoquinoline, which replaces one of the diphenylphosphino-naphthalene moieties and thus facilitates the oxidative addition of a sterically demanding secondary borane reagent. The structural modifications permitted by the synthetic route to phosphinoisoquinolines [50] makes it possible to synthesise analogous P,N ligands such as Phenap (**29**) [51] and 2-phenylquinazolin-4-yl-2-(diphenylphosphino)naphthalene (**30**) [52]. These P,N-type ligands were also coordinated to rhodium so that they could be applied in the hydroboration/oxidation reaction of vinylarenes (Table 6, entry 5-8). Nevertheless, the hydroboration reaction developed with these rhodium-analogous P,N ligand complexes achieved minor enantiomeric excesses. In addition, the efficiency of asymmetric hydroboration varies with the electronic properties of the substituents at phosphorus in Quinap derivates, [49c].



(S,R)-**27** (S)-**28** (R)-**29** (R)-**30** (R)-**31**

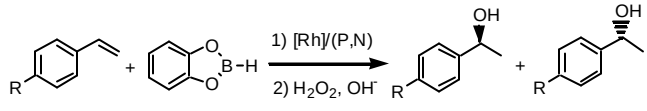
27a Ar= Ph

27b Ar=4-$CF_3C_4H_6$

Figure 4

Recently, Chan et al. developed a new atropoisomeric P,N ligand for rhodium-catalysed asymmetric hydroboration, called Pyphos (**31**) (Figure 4), [53]. When it was applied in rhodium-catalysed asymmetric hydroboration of vinylarenes, the enantiomeric excesses were similar to those of Rh-Quinap when the reaction was carried out at 0ºC (Table 6, entry 9-11).

Table 6. Catalytic asymmetric hydroboration of vinylarenes with Rh/(P,N ligand) complexes[a]



1 **(S)-2** **(R)-2**

Entry	Ligand (P,N)		R	T(^{0}C)	**2**(%)	e.e(%)	Conf.
1	**27**		H	20	76	94	R
2[b]	(S)-Quinap	**28**	MeO	20	95	94	S
3[b]	"		H	"	97	88	S
4[b]	"		Cl	"	98	78	S
5[b]	(R)-Phenap	**29**	H	0	94	67	R
6[b]	(R)-**30**		MeO		77	81	R
7	"		H	"	80	79	R
8	"		Cl	"	83	49	R
9	(R)-Pyphos	**31**	MeO	0	98	94	R
10	"		H	"	99	90	R
11	"		Cl	"	99	79	R

[a] Standard conditions. Solvent: THF, under argon, [Rh]: [Rh(cod)]$_2$]BF_4/(P,N); [b] [Rh]: [Rh(cod)(P,N)]BF_4

The regioselectivity in favour of branched alcohol product **2** does not depend on the electron-releasing or electron-withdrawing nature of the substituents in the phenyl ring of the substrates. However, the enantioselectivity shows slight differences, and is higher for electron-rich substrates than for electron-poor vinylarenes (Table 6). The Hammett plot of the e.e value of the hydroboration of several vinylarenes substrates obeys a linear free energy relationship [49c], [53-54], which suggests a simple trend related to the inductive effect of the substituents.

2.2. Catalytic cycles

The catalytic hydroboration reaction consists of several different steps. This introduction has shown that the hydroboration reaction can be catalysed with a wide variety of complexes for a significant number of substrates. The catalytic cycle then needs to be generalized although it is somewhat tricky. In addition, the nature of the catalytic complex, the steric and electronic properties of the substrate, the nature of the ligand, the solvent, the temperature, and the hydroborating reagent may have a significant effect on the mechanism of the hydroboration reaction catalysed with transition metals [55-58].

It seems clear that the mechanism of rhodium-catalysed hydroboration reactions is fundamentally different from that of the corresponding uncatalysed processes [59]. The role of the transition-metal complex in the process suggests that alkenes do not coordinate to the metal and that a free boron hydride does not attack the opposite π-face (Figure 5.a) because $^{2}\eta$-coordination deactivates alkenes toward electrophilic attack. On the other hand, the oxidative addition of the borane reagent to the metal makes the boron atom less electron deficient due to the electronic donation from metal *d* orbitals to boron. For this reason, it is assumed that hydride-η^{1}-borylrhodium complexes, likely intermediates in the catalytic cycle, are not added to free alkenes, as indicated in Figure 5.b. It might be concluded, then, that both the boron-hydride and the alkene are probably coordinated to the metal in the first steps of the rhodium-catalysed hydroboration.

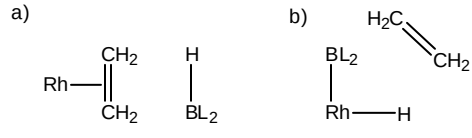
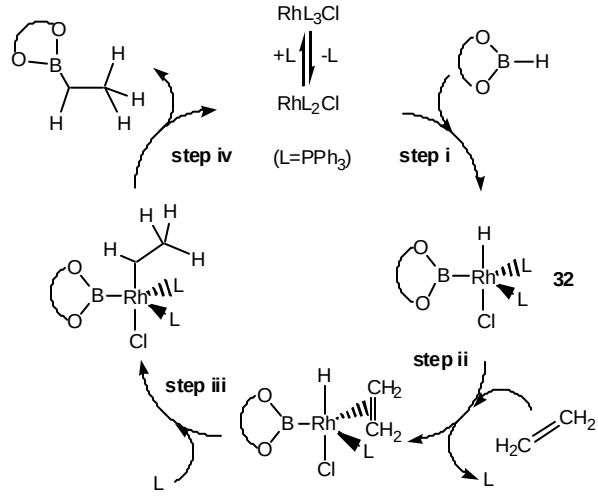


Figure 5

The transition-metal catalysed olefin hydroboration reaction using Wilkinson's catalyst $RhCl(PPh_3)_3$ with catecholborane has become an important and

well-established synthetic method [2]. Although the reaction was first reported by Männing and Nörth in 1985, an earlier key experiment by Kono and Ito led to the development of the catalytic transformation [60]. They demonstrated that B-H activation by Wilkinson's catalyst provides the hydride-η -borylrhodium complex **32**. As far as the catalytic mechanism is concerned, they proposed a dissociative pathway which involved oxidative addition of catecholborane to the rhodium complex (step i), followed by ethylene coordination with simultaneous dissociation of one PPh_3 group (step ii). Furthermore, migratory insertion of the olefin into the Rh-H bond (step iii), and reductive C-B bond coupling (step iv) (Scheme 6) could eventually provide the alkylboronate ester. Their suggested mechanism for $RhCl(PPh_3)_3$ catalysed hydroboration with catecholborane is analogous to that proposed for other, more thoroughly investigated rhodium-catalysed olefin addition reactions such as hydrogenation, hydrosilylation, and hydroformylation [61]. In the case of asymmetric



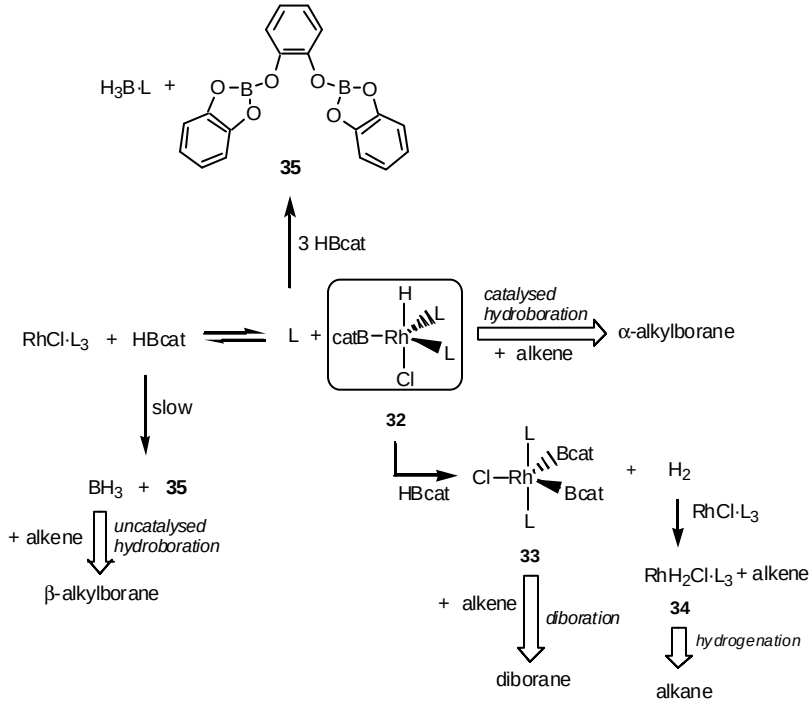
Scheme 6

hydrogenation, the relative stability of such key metal intermediates as hydridealkylrhodium, has given a detailed picture of the reaction mechanism [62]. Unfortunately, the intermediates in the hydroboration process are quite transient, at

least when catecholborane is used. Even though hydroboration is a relatively recent reaction, several in-depth studies of the catalytic hydroboration cycle have been published in the literature. Evans, Fu and Anderson [13] suggested a related and more detailed mechanism. According to this mechanism, results for deuterium labelling experiments of selected catalytic hydroboration reactions have been rationalised by reversible olefin complexation in Rh-H(D) bond and reversible hydride migration. Furthermore, the label distributions were different when these reactions were repeated by Burgess and van der Donk [12] with a commercial, partially oxidised, catalyst.

On the basis of their experiments, Burgess et al. [12] proposed an alternative associative mechanism which involves boron migration followed by β-H elimination, (also called 'dehydrogenative borylation'), as a competitive process in the catalytic hydroboration of hindered styrenes that yield vinylborane compounds CH_2=CH(BR_2). The vinylborane compounds were part of a complex mixture of products derived not only from catalysed hydroboration but also from uncatalysed hydroboration and the hydrogenation of alkenes, because the reaction of $RhCl(PPh_3)_3$ with catecholborane gives an unexpected mixture of borane and rhodium species (Scheme 7). The oxidative addition of catecholborane to $RhCl(PPh_3)_3$ affords a hydride-η^1-borylrhodium complex **32** [60], [63]. However, a second oxidative addition of the borane can carry out and generate H_2 and a diborylrhodium complex **33** [64]. The diboryl complex **33** can then undergo diboration or reductive monoborylation of alkenes, and the H_2 generated can hydrogenate alkenes. Thus, the hydroboration of RHC=CH_2 is often accompanied by the formation of small amounts of RCH(Bcat)CH_2(Bcat), RC(Bcat)=CH_2, RCH=CH(Bcat), and RCH_2CH_3, along with the desired hydroboration product. Therefore, the *in situ* degradation of catecholborane makes the reaction more complex when the catalysed reaction is very slow. In addition, the uncoordinated phosphine can react with catecholborane to yield $H_3B{\cdot}L$ and B_2cat_3 (cat=$O_2C_6H_4$) (**35**) [64]. Although the borane/phosphine adduct thus generated fortunately does not hydroborate alkenes, **35** may contribute to the production of other rhodium species, which have high catalytic activities similar to those of **32**. The reaction can also undergo competitive uncatalysed hydroboration with BH_3, and the formation of such hydroborated products does not reflect the true selectivity of the

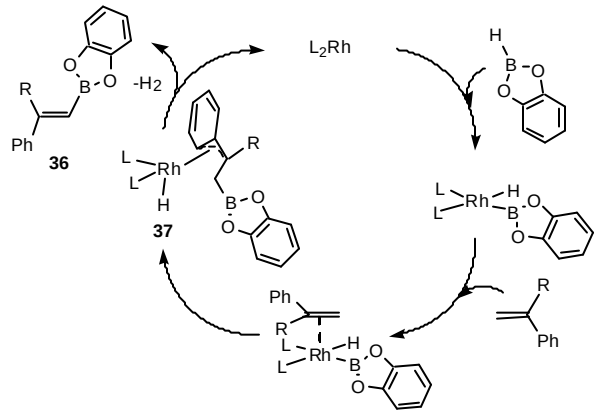
catalysed reactions [12], [28], [65]. The degradation of catecholborane to BH_3 and B_2cat_3 (**35**) is, in general, very slow at room temperature. However, the hydroboration with BH_3 can compete with the catalysed hydroboration even when the reaction is very slow, because the catalyst also decomposes and its activity is also low. Although many processes may generate side reactions, catecholborane undergoes clean hydroboration when the appropriate catalyst is selected.



Scheme 7

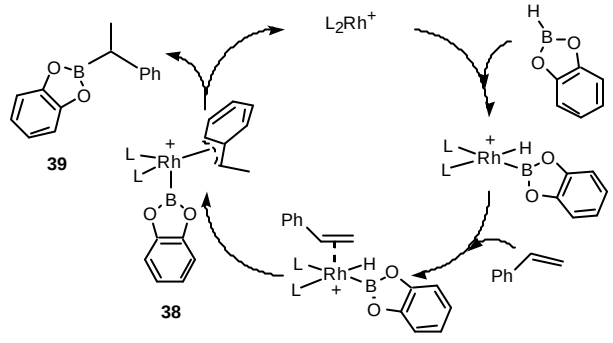
Westcott and Marder [56] have also contributed to this discussion with Burgess et al. [12]. They agreed with the 'dehydrogenative borylation' pathway which provides the vinylborane (**36**) (Scheme 8) subproduct. As far as the catalytic steps are concerned, the insertion of the alkene into the M-B bond can be followed by β-hydride elimination, which leads to the production of hydrogen. Formation of the hindered

tertiary alkylrhodium complex may be facilitated by formation of a $^{3}\eta$-benzylrhodium intermediate **37** (Scheme 8). Previously, Hayashi et al. have suggested that in the hydroboration of 2-phenylpropene with catecholborane, a $^{3}\eta$-benzylrhodium **38** complex may form and participate as an intermediate species in the catalytic cycle [15] (Scheme 9).



Scheme 8

Many authors have suggested that the rhodium-catalysed hydroboration reaction proceeds through a rhodium(III)/alkyl/boryl intermediate, which is formed by the oxidative addition of catecholborane to rhodium (I) followed by the insertion of alkene into the resulting H-Rh bond [2], [12-13] [60] (Scheme 6). Hayashi et al. [15] suggested that $^{3}\eta$-benzylrhodium complex **38** was a key intermediate in the catalytic cycle, after they observed the high regioselectivity obtained in the hydroboration of styrene (Scheme 9). In addition, they proposed that the vacant coordination site in the cationic rhodium intermediate, instead of neutral complexes, favours the formation of the $^{3}\eta$-benzylrhodium **38**. Finally, the reductive elimination step provided the branched borane (**39**) regioselectively.

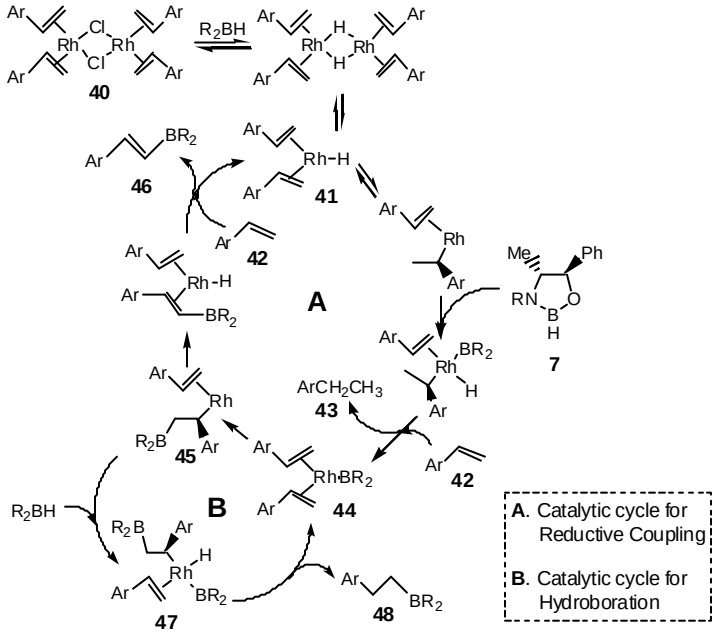


Scheme 9

In fact, it is difficult to present a general catalytic cycle for the catalytic hydroboration reaction, because of the important role of the nature of the catalyst, the borane and the substrate. Brown and Lloyd [24] studied the catalytic hydroboration of p-MeO-styrene by chiral borane **7** and the catalytic rhodium precursor **40** (Scheme 10). Under those catalytic conditions, the hydroboration of **42** yielded 50% of alkane **43** and 50% of vinylborane **46**. They proposed the mechanism shown in scheme 10, where the rate-limiting addition of B-H to rhodium led to the elimination of alkane and the formation of rhodium-boryl **44**. The vinylborane was then formed by β-migration of boron to coordinated alkene and β-elimination, which also regenerates hydriderhodium **41**. However, when the analogous reaction was carried out with catecholborane as the borane reagent, the hydroborated product was entirely the primary borane **48**. In order to explain their findings with catecholborane, they proposed a modified version of cycle A. Cycle B, then, involves catecholborane being added to intermediate **45** to give **47**, which eventually yields primary borane **48** with regeneration of **44** (Scheme 10).

Hydroboration has also been studied by theoretical methods. Morokuma et al. [66] focused on the associative mechanism of model reaction a), shown in equation 1. They found that the most favourable pathway involved oxidative H-B bond

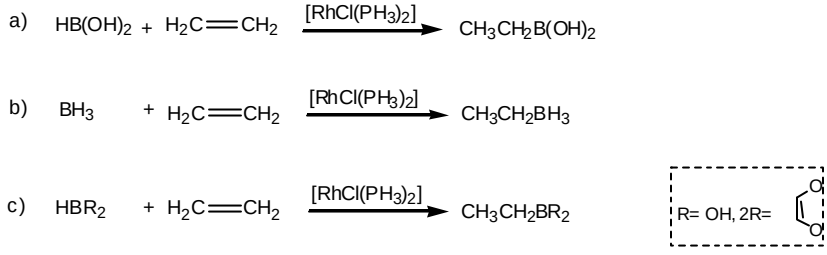
addition to $RhCl(PH_3)_2$ followed by the coordination of ethylene *trans* to chlorine, migratory ethylene insertion into the Rh-B bond, and finally reductive C-H bond coupling as the



Scheme 10

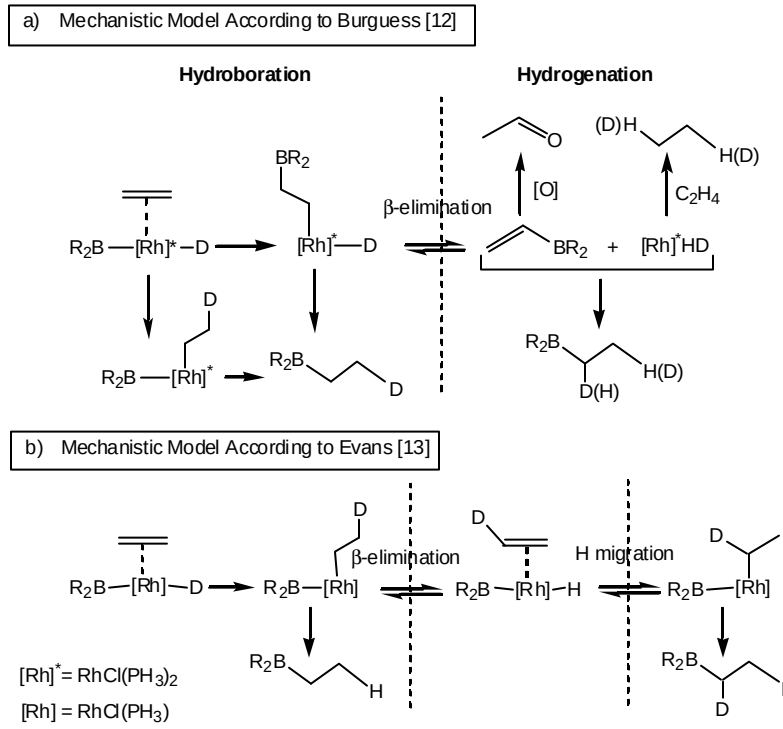
rate-determining step of the catalytic cycle. This last observation was in agreement with previous NMR studies by Burgess and Ohlmeyer [3a], who revealed that reductive elimination could be the slow step in overall formation. Subsequently, Dorigo and Schleyer made an *ab initio* study of the dissociative mechanism for model reaction b) illustrated in equation 1, where the model hydroborating reagent is simplified [67]. Their results supported the catalytic cycle originally presented by Mäning and Nörth [2]. They also excluded the possibility of an associative mechanism. Recently, Ziegler et al., [68] made a comparative study based on DFT type calculations of associative and dissociative mechanism of the model reactions c) shown in equation 1. They concluded that they agreed with Burgess et al. [12] on the

associative mechanism, and favoured the β-elimination for obtaining side products such as vinylboranes and alkanes. On the other hand, the dissociative mechanism in



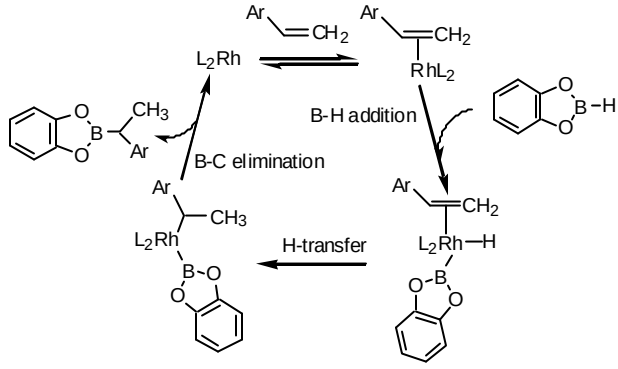
Equation 1

which hydride migration might be involved is in agreement with the mechanistic model of Evans [13]. According to calculations of Ziegler et al. [68], this mechanism might prefer the boron migration to the hydride migration (Scheme 11).



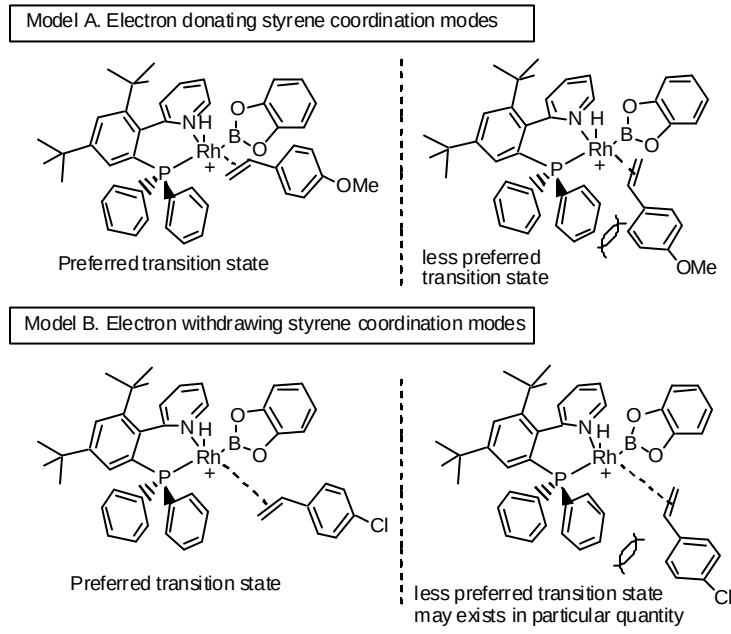
Scheme 11

In this context, Brown et al. suggested that the catalytic cycle for the hydroboration of vinylarenes follows the pathway in which the hydride could transfer regiospecifically to give the hydride $^{3}\eta$-benzylrhodium complex, which undergoes reductive elimination to the formation of the hydroboration product [49b]. A plausible complete sequence for the consecutive steps in the catalytic hydroboration cycle of vinylarenes is outlined in scheme 12. These steps are: 1) the reversible coordination of the alkene, 2) the oxidative addition of the catecholborane; 3) the hydride migratory insertion; and 4) the reductive elimination, which yields the final product and regenerates the catalytic active species. The same authors pointed out that the stereochemistry of hydroboration is rather general and predictable for various vinylarenes. They also suggested that the configuration of the new stereogenic centre could be determined in the hydride transfer step.



Scheme 12

Recently, Chan et al. [53] used the coordination of vinylarenes to the penta-coordinated Rh/H/(P,N)/catecholborane/vinylarene complexes to suggest that transition state models might explain the enantioselectivity observed in the hydroboration of electronically different vinylarenes (Scheme 13).



Scheme 13

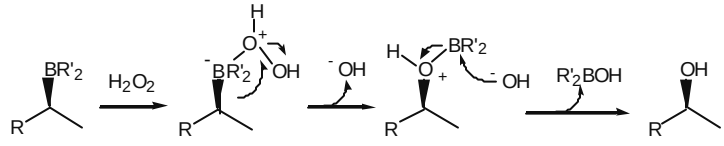
Vinylarenes with electron-releasing substituents might therefore coordinate more strongly *trans* to the pyridine moiety of the ligand than the vinylarenes with electron-withdrawing substituents. Therefore, the electron-rich substrates may be closer to the rhodium centre than their electron-poor analogues, thus providing better stereochemical communication and a higher enantioselectivity.

However, despite all these mechanistic approaches, the origin of the regio- and enantioselectivity of the catalytic hydroboration reaction has yet to be explained.

2.3. Synthetic applications

The high chemio-, regio- and enantioselectivity which might be imparted in one of the initial steps of the catalytic cycle, is coupled with the stereochemical integrity of the subsequent C*-X or C*-C bond forming stage. An interesting

application which has been used in numerous examples is the formation of C*-O bonds from C*-B bonds [3c], [15], [49c], [79-70], through the oxidation reaction. This transformation can be carried out because the alkylboronate esters react easily with a variety of neutral or negatively charge bases to form thermally stable adducts. Therefore, the oxidation of the borane involves the ambiphilic nucleophile hydroperoxide ion. This provides a 1,2-migration of an alkyl group from boron to oxygen with concurrent loss of the hydroxide ion. The step occurs with essentially complete retention of configuration (Scheme 14).



Scheme 14

The catalysed hydroboration reaction has been used in various synthetic applications because of its exceptional selectivities. The order of reactivity permits selective hydroboration at the terminal double bond in preference to other double bonds (Figure 6.a) [13], [71] or the ketone carbonyl group [3b] (Figure 6.b).

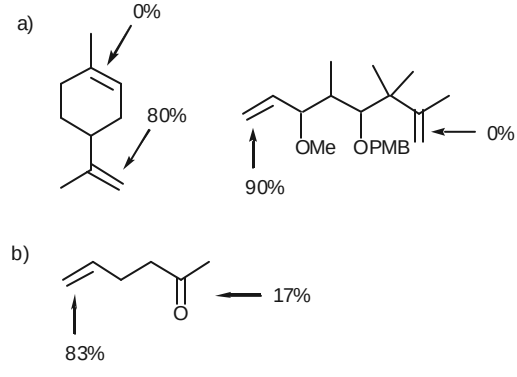
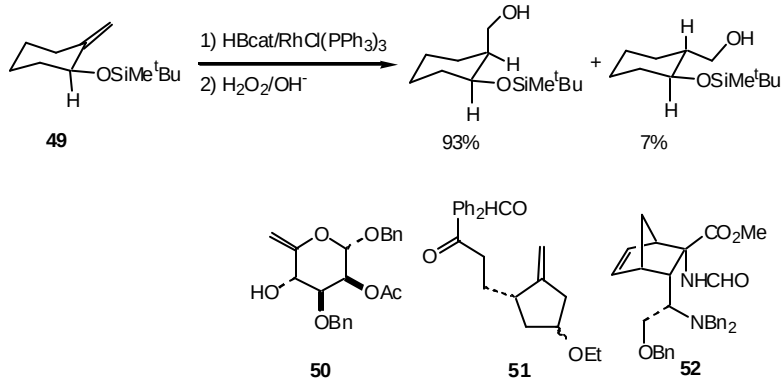


Figure 6

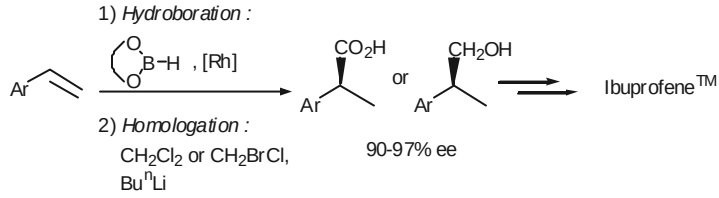
The hydroboration of *exo*-cyclic alkenes affords stereochemically complementary products between the catalysed and uncatalysed reaction (Scheme 15). Thus, the hydroboration/oxidation of **49** with 9-BBN yields two alcohols in a ratio of 39:61 in favour of the *trans* isomer. These results are in stark contrast to the catalysed hydroboration where the *cis*-alcohol is mainly produced (93%). This is because the catalysed reaction seems to be more sensitive to the steric effects than the electronic effects, whereas in the uncatalysed reaction the stereoelectronic effect prevails [72-74]. The high *cis*-stereo-selectivity observed in *exo*-cyclic alkenes can also be observed in various syntheses of natural products. Consequently, the alcohols obtained through the catalytic hydroboration/oxidation are used as precursors for the synthesis of several more complex compounds. For example, the catalysed hydroboration/oxidation reaction of **50** forms the antineoplastic Bleomycin A2 [75]. The catalysed hydroboration/oxidation of **51** leads to the sesterpene (+)-Luffariolide E [76], and the catalysed hydroboration/oxidation of **52** leads to the (-)-Altemicidin, which is an acaricidal and antitumor substance [77] (Scheme 15).



Scheme 15

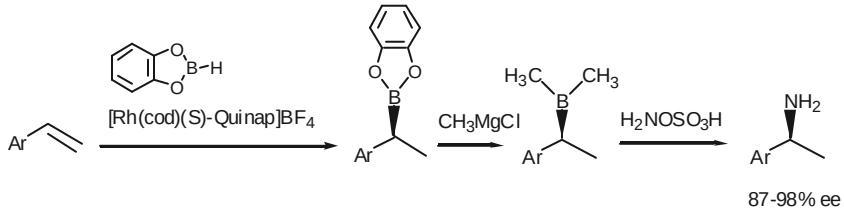
The one-carbon homologation of chiral alkylboronate esters has recently been demonstrated to occur also with complete retention of configuration, [78]. The catalytic asymmetric hydroboration-homologation sequence yields the

enantioselective synthesis of 2-aryl substituted carboxylic acids, which are of particular importance because they are non-steroidal anti-inflammatory agents such as Naproxen™ or Ibuprofen™. The latter can be synthesised as the enantiomerically enriched 2-arylpropionic acids shown in equation 2. The positive medicinal effects of these pharmaceuticals are ascribed to only one of the enantiomeric forms [79].



Equation 2

Another interesting asymmetric, two-step, “one-pot” reaction, in which catalytic asymmetric hydroboration is followed by an amination step, has made it possible to transform alkenes into chiral amines, through alkylboronate esters [80] (Equation 3).



Equation 3

Recently, Maeda and Brown have shown that the hydroboration/amination sequence can be used for the preparation of the antidepressant Sertraline using the Rh-Quinap catalyst complex [80d].

3. Recovery of the catalyst

Homogeneous catalysts generally provide higher activities, regio- and stereoselectivities than heterogeneous catalysts; in fact, most chiral catalysts are homogeneous. On the other hand, they are more difficult to separate, recover and reuse than the technically well established heterogeneous catalysts. The properties of these two catalytic systems are different but complementary so it could be very useful to combine their best properties. The heterogenisation or immobilisation of the homogeneous metal complex in an insoluble support makes it possible for the reacting organometallic complex to keep its high activities and selectivities and also to be recovered and recycled. Consequently, the catalytic complex can be separated from the products and unreacted reagents by an easy filtration, precipitation or phase separation [81-83]. Significant examples of different types of catalyst immobilisation, as well as their application in a variety of asymmetric reactions, have recently been reported [84-94]. However, chiral catalysts have also been immobilised in special liquid phases (aqueous, florous, ionic), occluded into membranes, or tethered to dendrimers. In this overview, we have focused on the immobilisation of catalytic complexes on solid supports.

The organometallic complex can be immobilised on an organic or inorganic solid support through different anchored or immobilised methods.

A wide variety of organic supports, (principally insoluble polymers) [95], take part in the common procedures for immobilising chiral ligands/catalysts. Although organic supports favour reaction rates that are higher than those of inorganic supports, the random distribution of the ligand units along the polymeric chain and swelling effects may be serious limitations. We have focused on the immobilisation of catalysts on inorganic supports, which are generally inert materials based on insoluble porous structures with a highly specific surface area. Amorphous oxides (in particular silica and, to a lesser extent, alumina) [96-97], zeolites [98-104], pillared clays, LDHs [105] and clay minerals (in particular, smectite laminar minerals) are most routinely used.

In general, immobilised single-site catalysts may be classified according to the nature of either the support material or the linkage between the support and the chiral ligand. Thus, the catalytic system can be immobilised by covalent binding, grafting by adsorption, grafting by ion-pairing, grafting by supported hydrogen-bond (SHB) and as a 'ship in a bottle' grafted catalyst. Figure 7 illustrates some of the immobilisation or heterogenisation strategies that have been described in the literature.

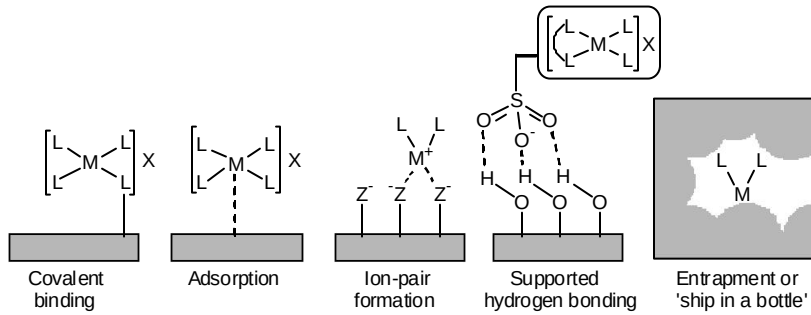


Figure 7

The *heterogenisation via covalently bound ligands* onto a solid support is one of the most frequent and versatile ways to heterogenise a chiral transition-metal complex. Both organic polymers and inorganic solids are useful supports here, although the latter have the advantage of being more robust and stable. The high stability of the covalent bond formed between the metal ligation and the support make the leaching of the catalytic complex more difficult. However, the most important disadvantage is that the ligand has to be functionalised, which means a long and delicate synthetic process and purification. Heterogenised catalysts are much more complex than their homogeneous counterparts and, therefore, generally, they often provide slight changes in activity and selectivity. In order to disturb the chiral induction as little as possible, the point of attachment of the tether to the ligand should be as far as possible from the stereogenic centre. The catalyst or ligands can be attached covalently onto the support via one-step or multistep functionalisation. The second methodology is the most efficient because it prevents the metal complexes from

dimerising and functionalises the ligand through a tether that is usually a linear chain that contains triethoxy- or methoxysilyl groups. The complex modified with the functionalised ligand is then anchored through the alkoxysilyl groups with the external silanols of the support (Figure 8).

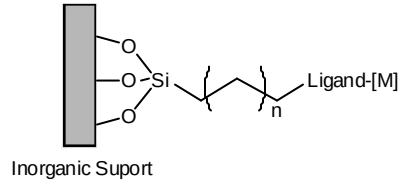


Figure 8

In 1994, Matlin et al. [106] presented an early example of a heterogeneous enantioselective catalyst that was even more active than its homogeneous counterpart. The β-diketone camphor was converted into their $SiCl_3$-derivative and the next step was the reaction between the functionalised ligand and the silanol groups of silica. The Cu-form of this complex was applied in the cyclopropanation of alkenes. The recuperation of catalyst was possible especially on those substrates, such as indene, where the side reaction of polymerization was absent.

Eisen et al. [107] and Kinting et al. [108] developed trimethoxysilyl-functionalised di-Rh-complexes, which reacted with silica to be immobilised. The heterogenised catalysts gave greater stability than their homogeneous forms and were applied to catalyse the asymmetric hydrogenation reaction of prochiral unsaturated acids and esters. Although the heterogenised catalytic system proved to be enantioselective in the first run, leaching of the metal was observed. Corma and coworkers anchored Rh-complexes through the triethoxysilyl groups contained in modified bidentate amino acid ligands, both on silica and on USY-zeolite [109-110]. The complex anchored via the covalent bond to the zeolite showed a higher activity for alkene hydrogenation and a considerable increase in enantioselectivity (>95%) in the hydrogenation of ethyl (Z)-α-benzoylaminocinnamate. This introduced a new concept: the important role of the steric limitation of the support. The zeolite

supported catalyst was reused several times with no loss in activity or metal content. In addition, no induction period was required, probably as a consequence of the concentration effect of the zeolite and the interaction of the catalyst with the electrostatic fields present in the zeolite, which assist the formation of the catalytic active species. Also, Johnson et al. [111] observed a positive confinement effect of the support because the results obtained with MCM-41 were significantly better than when a silica support was used. The heterogenised Pd-ferrocene catalyst showed high conversions and e.e in the allylic amination of cinnamyl acetate. Surprisingly, the regioselectivity changed drastically.

Ferrocenyldiphosphine complexes were first functionalised with suitable silylating agents before they were attached to a variety of supports. They have been used with relative success in the heterogenised hydrogenation of imines for Ciba-Geigy [112].

Mayoral et al. [113] studied the Diels-Alder reaction catalysed by chiral Lewis acids immobilised on alumina and silica. The best strategy was to use the metal and not the chiral auxiliary to graft the Lewis acid onto the solid. This decreased the influence of the conformation of the chiral auxiliary and hence affected the stereochemistry of the reaction.

Recently, several reactions have been developed with heterogenised catalytic systems prepared via covalent anchoring principally to silica, or other inorganic supports (such as USY-zeolites, or mesoporous MCM-41). Some of these reactions are the following: cyclopropanation [114], hydrogenation [114], [115], hydroformylation [115], olefin polymerization [116], asymmetric addition of diethylzinc to benzaldehyde [117], sulphide oxidation [118], Suzuki cross-coupling [119], cyanosilylation of aldehydes [120a], epoxide ring opening [120b], olefin metathesis [121a, b] and epoxidation of cyclohexane [121c]. All these heterogenised systems carried out an active and, in the case of the asymmetric reactions, selective performance which, in addition, was recycled and re-used in numerous catalytic cycles without loss of conversion or enantiomeric excess.

Augustine and coworkers proposed a new technique for anchoring homogeneous catalysts to a support material without having to modify the ligand [122]. In this way, the reactivity and selectivity of the corresponding homogeneous

catalyst is retained even on re-use. The original immobilisation procedure, called *three-component inorganic systems*, consists of a preformed metal complex grafted to a solid support through an anchoring agent (Figure 9).

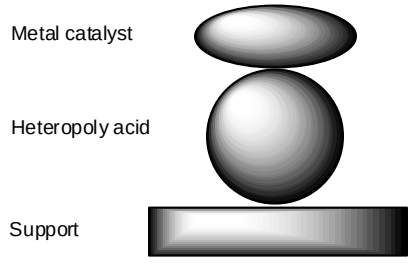
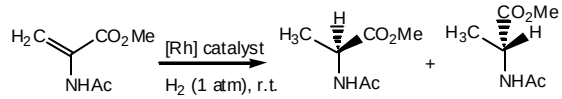


Figure 9

The anchoring agents are heteropoly acids [123] (phosphotungstic acid (PTA), phosphomolybdic acid, silicontungstic acid, silicomolybdic acid), which can be attached to several supports (alumina, carbon, lanthana, montmorillonite K) by interaction of the acidic protons of the acid with basic sites on the support. Although the nature of the bonds is not clear, it has been suggested that the metal (Rh, Ir) is attached to the heteropoly acid by the oxygen atoms on its surface [124].

Augustine and coworkers applied the supported-heteropoly acid-metal catalyst technique to the hydrogenation reaction of methyl-2-acetamidoacrylate (**53**) with rhodium catalyst complex. The results were best with the Rh(DiPAMP)/ /PTA/Montmorillonite K catalyst, (Table 7). In the first run, the immobilised catalyst was less active and selective than the homogeneous one. However, when this catalyst was reused for this reaction, it became more active and selective, and retained the same activity and selectivity for 15 consecutive runs.

Table 7. Enantioselectivity data from multiple consecutive hydrogenation reactions[a]



53 **(S)** **(R)**

Cat. system	Run	ee (%)
Homog. Rh/L-L	-	76
Rh/L-L/PTA/MK[b]	1	67
	2	92
	3	94
	6	96
	9	97
	15	97

[a] Standard conditions: at 25 ^{0}C under 1 atm H_2, 20 μmol of supported catalyst, 0.8 mmol of **53** for each run; [b] L-L: (DiPAMP), PTA: phosphotungstic acid, MK: montmorillonite K.

The *heterogenisations via entrapment or encapsulation*, also often related with the 'ship in a bottle' concept, involves two different preparative strategies to immobilise transition-metal catalysts in the cavities of a solid support. The encapsulation is based on building up catalysts in well-defined cages of porous supports [125-126], and entrapment consists of building up an inorganic sol gel [127] or organic polymeric network around a pre-formed catalyst. Encapsulating a transition metal complex in cages of a support fully depends on the respective size of the metal complex and the cage, to prevent leaching during reaction, [128]. The zeolites are excellent candidates for this immobilisation because of their dimensional and regular pores or cages. The encapsulation of chiral Mn(salen) complexes in zeolites, which are then applied in the epoxidation reaction of alkenes, was described simultaneously by two groups, who used Y and EMT zeolites as solid supports. Corma and coworkers developed a smaller salen complex without *tert*-butyl groups, which were immobilised in a zeolite Y [126]. This immobilised catalyst system restricted the diffusion of the substrate and products through the micropores of the solid, and

decreased the reaction rate. In addition, the heterogenised catalytic system showed a slightly reduced performance in asymmetric induction. This was interpreted as a combination of a non-catalysed, epoxidation reaction in the liquid phases and/or the existence of residual amounts of non-complexed Mn^{2+} acting as the catalytic system. However, the study by Bein et al., which used larger cages of the EMT-structure allowed positions 5 and 5' to accommodate larger complexes bearing methyl groups and 3 and 3' to accommodate *tert*-butyl groups [125]. The activities of the heterogenised catalysts were lower than those of the homogeneous catalysts, too, but the enantioselectivity was unchanged. Table 8 compares the catalytic behaviour of the homogeneous and heterogeneised catalytic systems for the asymmetric epoxidation reaction.

In 1996 Capka and coworkers immobilised Rh-complexes onto silica and alumina via entrapment in a hydrophobic surface layer [129]. On comparing the activity and enantioselectivity of the immobilised catalyst with the analogous homogeneous counterpart, they found that the heterogenised catalytic system performed better. Recycling experiments kept the enantioselectivity constant, but the activity decreased gradually during the subsequent cycles, probably due to leaching of the rhodium complex.

Table 8. Asymmetric epoxidation of *cis*-β-methylstyrene catalysed by Mn–salen complexes.

Catalytic system	C(%)	Epoxide selectivity (%)	e.e (%)[c]
(salen)$Mn^{III}Cl$ [a]	28	100	74
(salen*)$Mn^{III}Cl$ [b]	85	97	80
(salen)Mn^{III}-Y [a]	5	76	58
(salen*)Mn^{III}-EMT [b]	15	67	80
(salen*)Mn^{III}-EMT [b]	47	58	88

[a] salen= *trans*-(R,R)-1,2-bis(salicylideneamino)-cyclohexane. Epoxidation run at 5^0C, 2h, CH_2Cl_2, 5%(salen)$Mn^{III}Cl$ or 15h with 90g (salen)Mn^{III}-Y (3.8% complex content); [b] salen*= (S,S)-N,N'-bis(3-*tert*-butyl-5-methylsalicylidene)-cyclohexanediamine. Epoxidation run at 0^0C, 1h, CH_2Cl_2, 5% catalyst complex; [c] (S, R) Configuration.

The polydimethylsiloxane (PDMS) is an organic-inorganic support. PDMS is formed by an inorganic backbone which contains short organic side chains. It was used as a support in the immobilisation processes of catalytic systems, via entrapment, carried out by Jacobs. A promising example was reported by Jacobs' group, who entrapped Jacobsen's Mn-salen epoxidation catalyst in PDMS. The epoxidation of 1,3-cyclooctadiene with this catalytic system provided an enantiomeric excess of 50% [130], and Noyori's Ru-Binap hydrogenation catalyst immobilised in PDMS provided 92% of enantiomeric excess for the hydrogenation of methyl acetoacetate in the presence of toluene-*p*-sulfonic acid [131]. Leaching depended heavily on the size and the solubility of the metal complex and the swelling of the polymer [132].

Recently, a new heterogenisation strategy has been reported: *heterogenisation via supported hydrogen bonding (SHB)*. It is a non-covalent method for preparing silica-immobilised metal catalysts for use in solid-liquid reactions with apolar solvents [133-135]. The terminal silanols of different types of silica interact with the oxygen atoms of sulfonate groups from both phosphine ligands contained in the metal complex or triflate counter-anion. The transition metal catalyst is linked to the support only through a hydrogen bonding interaction. Different types of chiral catalysts have been immobilised with this technique: i) zwitterionic cationic complexes of ruthenium with triflate as counter-anion, [(sulphos)Ru(NCMe)$_3$]OTf (Figure 10.a), [133], [134], ii) zwitterionic neutral complexes of rhodium (I) such as [Rh(cod)(R,R)-BDPBzPSO$_3$)] (Figure 10.b), [135], iii) cationic complexes of rhodium(III) containing a triflate counter-anion, [Rh(nbd)(P,P)]OTf where (P,P)= (S)-Binap, (R,R)-Me-DuPHOS, (R,R)-Diop (Figure 10.c) [136]. Types i) and ii) are examples of the immobilisation of the optically active rhodium diphosphine complex. This immobilisation involves that the sulfonate group must be introduced into the chiral ligand previously. In contrast, cationic complexes stay close to the silica surface by hydrogen-bonding interactions and by electrostatic interactions with the triflate ions which, in turn, are immobilised on the support via hydrogen bonds. On the other hand, no immobilisation at all was observed when the triflate anion (Figure 10.c) was replaced by counter-anions that cannot interact through hydrogen bonds such as BPh_4^-, BAr_F^- [136]. The chiral SHB rhodium catalysts have been applied in the enantioselective hydrogenation of

prochiral olefins, particularly itaconates and 2-acetamido acrylates [135], [136], in *n*-heptane and *n*-hexane. The conversions were generally similar to those of the homogeneous reaction. Moreover, unlike the analogous homogeneous reactions, the immobilisation of the chiral precursors on silica did not reduce asymmetric induction and in some cases it even increased it. No metal leaching was observed in several consecutive runs. In addition, effective catalyst recycling meant that the catalytic system remained active and enantioselective.

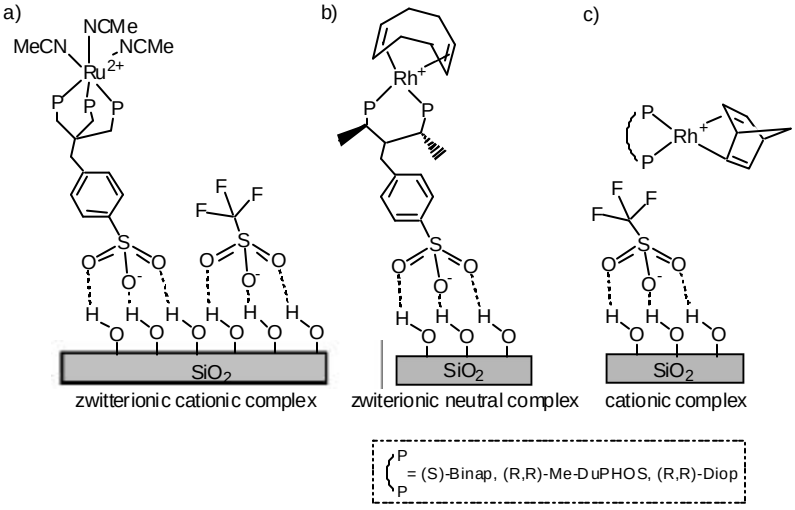


Figure 10

Redge and coworkers [136] made an interesting study of the non-covalent immobilisation of [Rh(cod)(R,R)-Me-(DuPHOS)]OTf onto mesoporous silica, such as MCM-41. The NMR spectroscopy of ^{31}P and ^{19}F nucleus indicated that there is an interaction between the support and the triflate ($^{-}SO_3CF_3$), probably through hydrogen bonding similar to that demonstrated by Bianchini's group.

Pérez and coworkers have suggested a different immobilisation via the hydrogen bond method [137]. They proposed a complex interaction through classical hydrogen bonds and nonclassical dihydrogen bonds between a preformed

polypyrazolylborane copper(I) complex and silica, for the olefin cyclopropanation reaction (Figure 11). The external silanol groups of the silica can interact via a hydrogen bond with the NH of the ligand. In addition, the B-H bonds of the ligand are available to interact with the silica surface via a DHB (dihydrogen bond) O-H···H-B similar to the one found by Crabtree et al. in the molecules of BH_3NH_3 [138]. Initially, leaching was present during the catalytic process, but it was minimised by using an appropriate solvent. The catalyst was reused with no significant loss in the catalytic activity for 10 consecutive cycles.

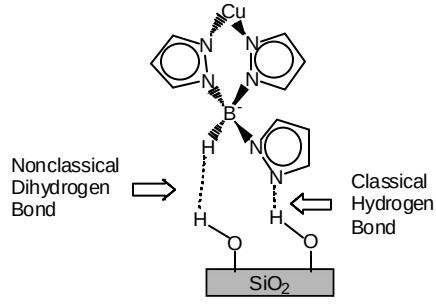


Figure 11

In most cases, the immobilisation requires the functionalisation of the ligands, such as in the covalent bonding or in some cases of the supported hydrogen bonding (SHB) immobilization. From a practical point of view, the *heterogenisation via adsorption or ion-pair formation* is simpler, because very often the chiral ligand does not need to be altered [139-140]. Consequently, the integrity of the chiral ligand can minimise the different activities and selectivities expected between the performance of the homogeneous and hetereogenised catalytic systems.

The adsorption and ion-pair formation immobilisation protocols usually take advantage of the properties of the support. However, occasionally ion-pair formation needs the support to be modified, for example by creating charges on silica via the functionalisation of the silylating groups (Figure 12.a) [141], or by modifying the ligand as the sulfonated Binap complex (bearing 4 negative charges) to be retained in LDHs via coulombic interactions (Figure 12.b) [142].

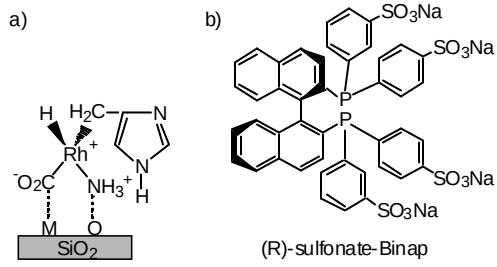


Figure 12

Taking into account the importance of the support we have focused on the smectites clay's group.

Smectite clays, such as montmorillonite K and bentonite, have recently attracted interest as supports for the heterogenisation homogeneous catalysts, because they have a combination of cation exchange, intercalation and swelling properties which makes them unique [95b], [143]. Smectites are a family of clays mainly consisting of hydrated sodium calcium aluminium silicate, the chemical formula of which is $(M^{n+}{}_{x/n})\cdot yH_2O[Al_{4.0-x}Mg_x]_O[Si_{8.0}]_T\ O_{20}(OH)_4$. Their basic structural unit is the tetrahedron SiO^{-4}. This mineral clay is constructed of a single octahedral sheet sandwiched between two tetrahedral sheets, with the octahedral sheet sharing the apical oxygens of the tetrahedral sheet. In the case of bentonite and montmorillonite, the octahedral sheet may be dioctahedral (only 2/3 of the octahedral positions are empty) (Figure 13). A layer charge is created by substitutions in either the octahedral sheet (typically by the substitution of low-charge species such as Mg^{2+}, Fe^{2+}, or Mn^{2+} for Al^{3+}) or the tetrahedral sheet (where Al^{3+} or occasionally Fe^{3+} substitutes for Si^{4+}), which produce one negative charge per substitution. They have a charge deficiency in either the octahedral or tetrahedral layer. The neutrality of the smectite crystalline structure or structural unit is obtained by the adsorption of exchangeable cations (either anhydrous or hydrated) in the interlayered space, generating its cation-exchange capacity (capacity of reversible exchange of cations). The usually reversible exchangeable cations are: Na^+, K^+, Ca^{2+}, Mg^{2+}, rarely Al^{+3}, Fe^{3+} or Fe^{2+}, and H_3O^+. The differences in the smectite compositions cause the

diversity in the family. In addition, their principal properties (intercalation, laminar swelling, ionic exchange, and adsorption capacity) are related to their composition and structural characteristics. Consequently, the immobilisation process is different for each smectite.

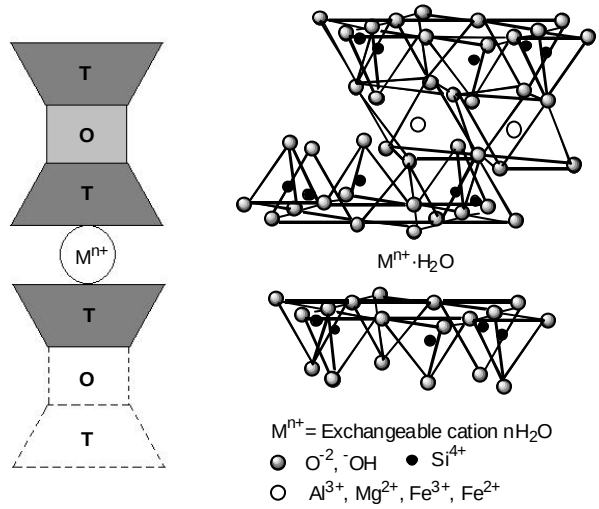


Figure 13

In previous projects [144], our group has studied the immobilisation process of the organometallic complex [M(cod)(P,P)]X on montmorillonite K-10 (MK-10) through the adsorption of the catalyst on the external surface. The crystalline structure of bentonite (BDH), which has the same chemical composition, means that it has a considerable cationic exchange capacity (Figure 14). Crocker and Herold [145] suggested that montmorillonite and bentonite clay minerals behave differently because of structural differences. The MK-10 is obtained via an aggressive acid treatment of the natural BDH smectites. As a result, the octahedral layers of the clay are partially destroyed and the lattice negative charge is partially suppressed and the crystallinity of the solid is reduced. Thus, MK-10 increases the surface area and favours the adsorption capacity over the ionic exchange properties.

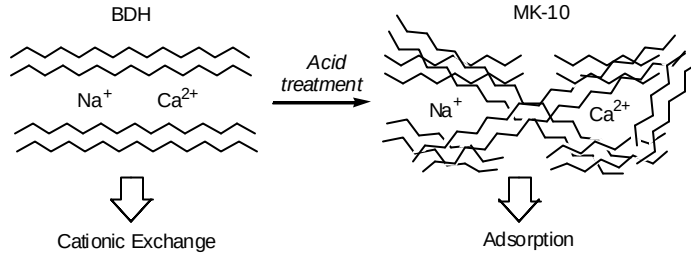


Figure 14

Most of the applications of the catalytic systems immobilised via ion exchange or adsorption have been carried out in reduction (mainly hydrogenation) [91], [146], reductive alkylation of amines [144c] cyclopropanation reactions [139], [147], and cyclocarbonylation reactions [148]. More recently, studies of other reactions involving C-C bond formation, such as Heck [149], have been added to the list of applications.

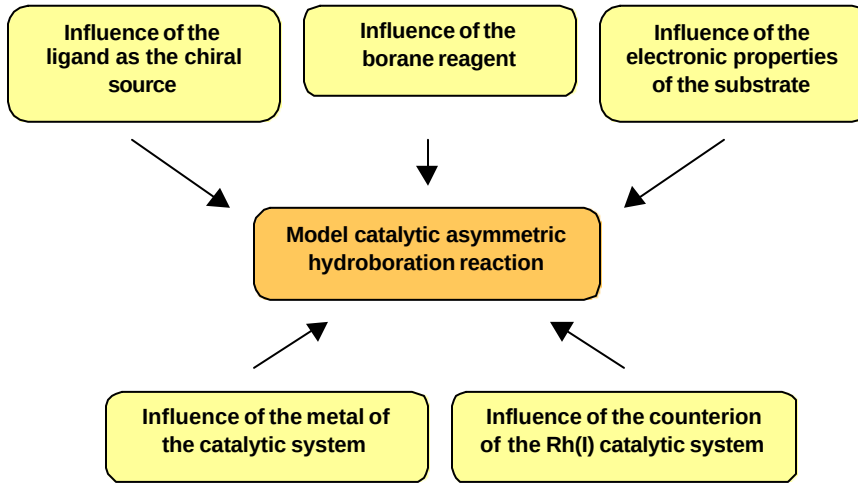
4. Scope of this thesis

This introduction clearly shows the interest in the catalytic asymmetric hydroboration reaction. The effort that various authors have made to develop chiral catalytic systems for this transformation has been rewarded by obtaining excellent catalytic performances. It is also noteworthy the intense dedication to develop an environmental and economic viability of chemical transformations through the design of catalytic systems that can be removed and reused.

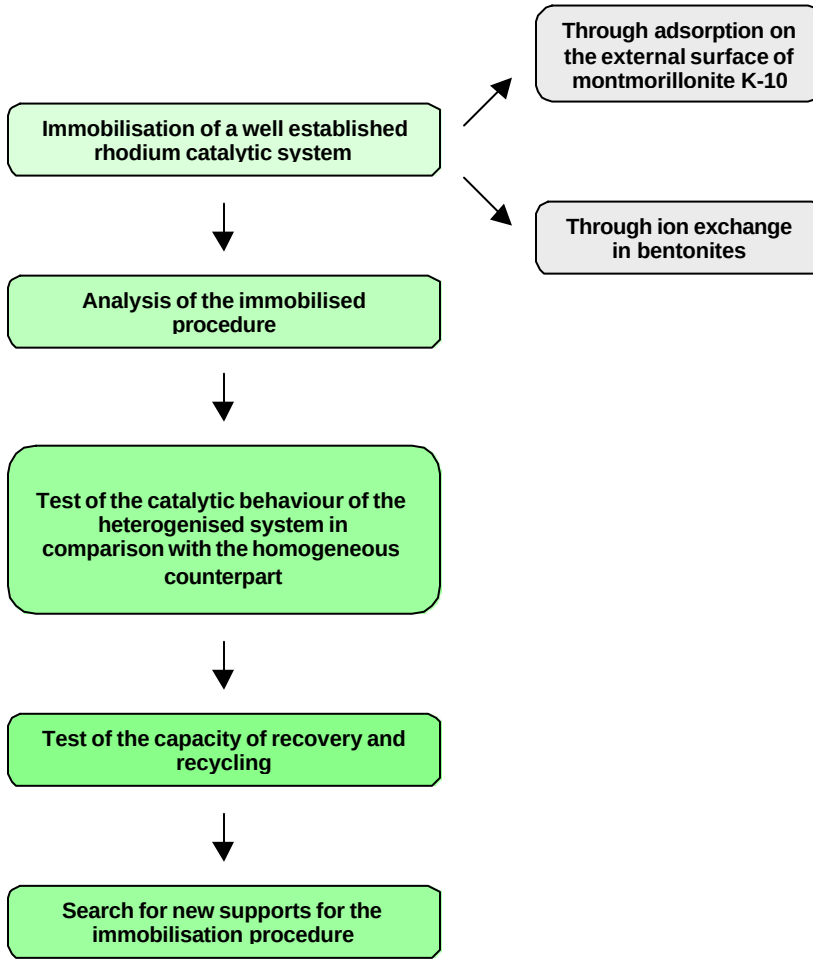
At this point, we planned to develop in this thesis the following aspects:

1) Understand how high activity and selectivity can be generated throughout the hydroboration process.

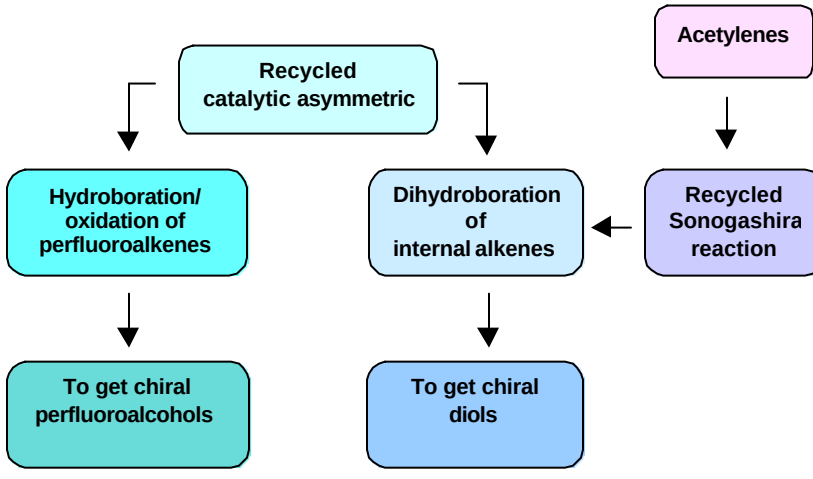
To create an overall picture of the various influences on the catalytic asymmetric hydroboration reaction, we take into account a model reaction where the substrate is styrene, the catalytic system is a cationic rhodium complex, the source of chirality is the atropoisomeric P,N ligand Quinap, and the borane reagent is catecholborane. To facilitate the analysis, we fixed the reaction conditions and oxidised the hydroborated products to alcohols, before initiating the following systematic study:



2) Design of a chiral catalytic system that can be easily recovered from the products and reused in the catalytic asymmetric hydroboration reaction, and which responds to the challenge of improving the environmental and economic viability of the asymmetric process



3) Extension of the accumulated know how on chiral organoboron compounds to other substrates. In particular we focused on:



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