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The Role of Secondary Interactions in the Asymmetric Palladium-Catalysed Hydrosilylation of Olefins with Monophosphane Ligands

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Abstract: A structure-activity survey of monophosphane ligands used in the asymmetric palladium-catalysed hydrosilylation reaction of olefins is presented and used to assess the role of secondary interactions on catalyst activity and selectivity.

Keywords: alcohols; asymmetric catalysis; hydrosilylation; phosphane ligands; secondary interactions

1 Introduction

The asymmetric functionalisation of prochiral olefins is an area of organic synthesis that continues to attract widespread interest.[1] Enantioselective addition of hydrosilanes across carbon-carbon double bonds, termed the asymmetric hydrosilylation (AHS) reaction, is one important example. The AHS provides a useful gateway to optically active alcohols *via* the Tamao oxidation,[2] in which the carbon-silicon bond is converted to a carbon-oxygen bond with retention of configuration at the carbon centre.

Phosphane ligands have played a key role in asymmetric catalysis ever since the pioneering work of Knowles[3] and Horner[4] in the late 1960s. Much of the research since then has focused on the development of bisphosphanes as chelating ligands for use in asymmetric catalytic reactions.[5] A major breakthrough in AHS chemistry, however, was the recognition that a monophosphane-palladium combination was a necessary requirement for an active catalyst.[6] Since this realisation, the design, synthesis and testing of new monophosphane ligands has been stimulated by the search for potent and selective catalysts for AHS reactions. The literature on this subject has been covered in several comprehensive surveys.[7] The intention of this review is to analyse the performance of a wide range of ligands, relating structural features to activity and selectivity in the AHS. A particular focus will be on the role of secondary donation, i.e., interactions other than that of the primary phosphane donor to the palladium metal.

2 Ligands with Well-Defined Secondary Donors

Enantiomerically pure ligands based on ferrocenyl scaffolds have proven so successful in asymmetric catalysis that they are now recognised as so-called "privileged ligands".[8] In an early report[9] the phosphane-amine palladium complex **1**, easily synthesised from Ugi's amine **2**[10] *via* ligand **3**, was used by Hayashi and co-workers to catalyse the asymmetric hydrosilylation (AHS) of styrene (Scheme 1). A reaction temperature of 70 °C gave a >95 % yield of the product benzylic silane which, upon oxidation to α-methylbenzyl alcohol, was found to have an *ee* of 52 %. A similar result was obtained when norbornene was subjected to identical conditions. It is postulated that the relatively high reaction temperature required for these reactions (70 °C), compared to many of the reactions described herein, is a reflection of the energy required to create a vacant coordination site on the metal centre by dissociation of the nitrogen-palladium bond.

Hayashi subsequently introduced polyfluoroalkyl groups onto the amine donor,[11] and converted the resulting ligands into palladium complexes **4** and **5** (Scheme 2). It was found that whilst catalyst **1** was inactive for the AHS of cyclopentadiene (entry 1), catalysts **4** and **5** gave significant yields (73 and 41 %) and enantioselectivities (57 and 55 %) operating at temperatures as low as 25 °C (entries 2 and 3). The authors attributed the increased activity of **4** and **5**, at least in part, to their improved solubility at ambient

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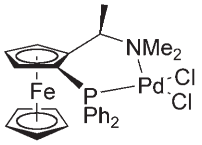
Matthew Rudd obtained his M.Sci. from King's College London before moving to Imperial College London to study for his Ph.D. with Professor Gibson. His research interests are focused on the synthesis of novel monophosphanes and their ability to sustain and direct asymmetric transition metal-catalysed reactions.



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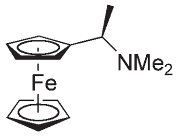

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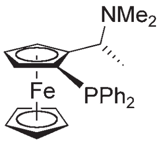

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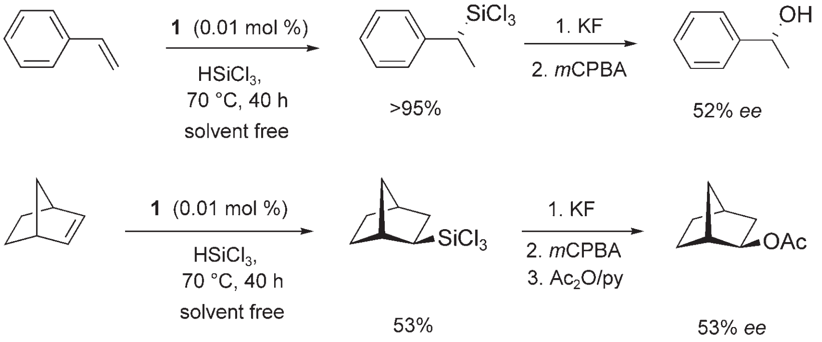
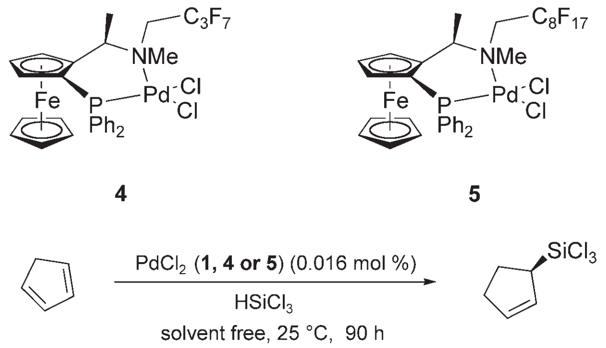


Scheme 1. Catalyst **1** is active at 70 °C.

temperature compared to **1**. However, it is also possible that the presence of the fluorous tail attenuates the coordinative power of the amine and weakens the chelation thus allowing catalysis to proceed more readily.

The AHS of cyclohexadiene using a variety of chiral ligands was investigated by Ohmura (Scheme 3).[12] Ligand **3** gave a low asymmetric induction of 9% *ee* (entry 1) at room temperature, but replacement of the dimethylamino group with a range of alkoxy groups led to significant improvements in enantioselectivity (it is worthy of note here that palladium has a greater affinity to nitrogen donors than to oxygen donors). Methoxy- and ethoxy-PPF, **6** and **7**, respectively, both gave 54% *ee* under identical conditions (entries 2 and 3), whilst employment of the electron-deficient trifluoroalkoxy-PPF **8** raised the enantioselectivity still further (65% *ee*, entry 4). The effectiveness of an oxygen donor was emphasised by the successful results obtained with PPF-OH **9** (72% *ee*, entry 5) and PPF-OAc **10** (entry 6).

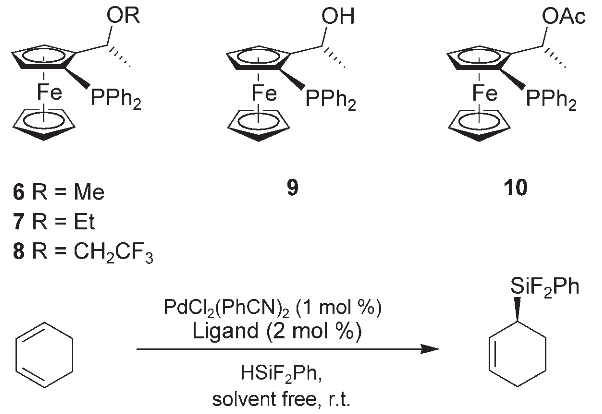
From the results described so far, it is clear that the nature of the functionalised side chain has an impact on the activity and selectivity of the AHS catalyst. Furthermore, lowering the co-ordinative power of the secondary interaction appears to have a beneficial effect on activity and selectivity. It is interesting in this context to note the results obtained more recently by Hayashi, employing the bisPPF-OMe ligands **11**–**13** for the AHS of 1,3-dienes (Scheme 4).[13] It was



Entry	Catalyst	Yield [%]	*ee* [%]
1	**1**	0	n/a
2	**4**	73	57 (*R*)
3	**5**	41	55 (*R*)

Cyclopentadiene:$HSiCl_3$:catalyst = 1:1.25:0.00016.

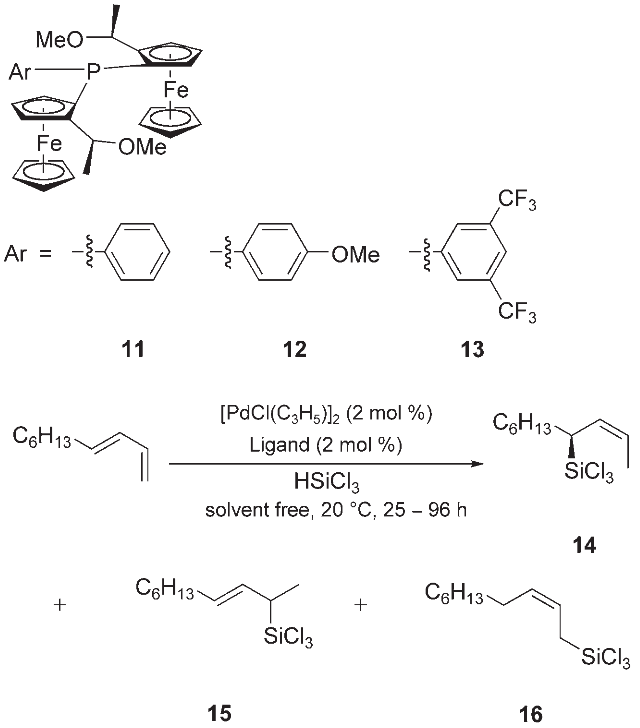
Scheme 2. Catalysts **4** and **5** are active at 25 °C.



Entry	L	Time [h]	Yield [%]	*ee* [%]
1	**3**	62	45	9 (*S*)
2	**6**	20	50	54 (*S*)
3	**7**	46	54	54 (*S*)
4	**8**	42	57	65 (*S*)
5	**9**	42	63	72 (*S*)
6	**10**	20	31	62 (*S*)

Cyclohexadiene:$HSiF_2Ph$:Pd:Ligand = 1:2:0.01:0.02. Overall yields are based on cyclohexadiene.

Scheme 3. Oxygen secondary donors give more active and selective catalysts than amine secondary donors.



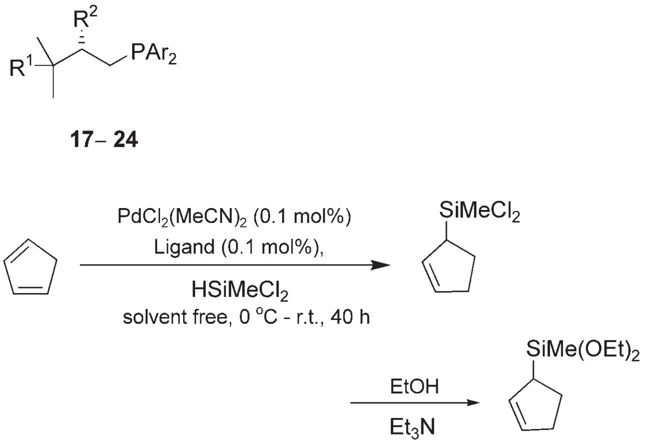
Entry	L	Time [h]	Yield [%][a]	**14**:**15**:**16**	*ee* **14** [%]
1	**11**	29	78	90:9:1	76 (*S*)
2	**12**	96	43	82:3:15	68 (*S*)
3	**13**	25	91	87:10:3	87 (*S*)

Deca-1,3-diene:$HSiCl_3$:Pd:Ligand = 1:1.2:0.01:0.02.
[a] Yield of mixture of **14**, **15** and **16**.

Scheme 4. Reducing the co-ordinative strength of the primary donor is also beneficial.

found that the relatively electron-rich anisylphosphane **12** gave a sluggish reaction and moderate enantiomeric excess for the AHS of deca-1,3-diene (entry 2) with respect to the simple phenyl analogue **11** (entry 1), whereas the electron-poor phosphane **13**, containing trifluoromethyl groups, was much more active giving the product allylsilane with up to 87% *ee* (entry 3). Lowering the coordinative ability of the primary donor, in this case it seems, is also beneficial to enantioselectivity.

Achiwa and co-workers prepared chiral (β-aminoalkyl)-phosphane derivatives[14] based on the (*S*)-valinol skeleton. An initial study focused on ligands analogous to those previously studied on Ugi's ferrocenyl scaffold, namely phosphine-amines **17–19.** It was found in the case of **17** (a direct analogue of **3**) that a moderate yield and poor selectivity were obtained for the AHS of cyclopentadiene (Scheme 5, entry 1). Ligand **18**, with increased electron density at phosphorus, was less active, and ligand **19** with lowered electron density at phosphorus was more active; both displayed neglible enantioselectivity (entries 2 and 3). Ligand **20**, containing an oxygen secondary donor, gave a catalyst of good activity and moderate enantioselectivity (37% *ee*, entry 4).



Entry	Ligand	R^1	R^2	Ar	T [°C]	Yield [%]	*ee* [%]
1	**17**	H	NMe_2	Ph	r.t.	60	(*R*)[a]
2	**18**	H	NMe_2	$4\text{-}OCH_3C_6H_4$	r.t.	37	(*R*)[a]
3	**19**	H	NMe_2	$4\text{-}ClC_6H_4$	r.t.	78	(*R*)[a]
4	**20**	H	OCH_2OCH_3	Ph	0	87	37 (*R*)
5	**21**	H	$NHSO_2CH_3$	Ph	0	82	61 (*S*)
6	**22**	H	$NCH_3SO_2CH_3$	Ph	0	84	7 (*S*)
7	**23**	H	$NHSO_2CF_3$	Ph	0	84	72 (*S*)
8	**24**	Me	$NHSO_2CH_3$	Ph	0	84	68 (*S*)

Cyclopentadiene:$HSiC_{l2}Me$:$PdCl_2(CH_3CN)_2$:Ligand = 1:2:0.001:0.001.

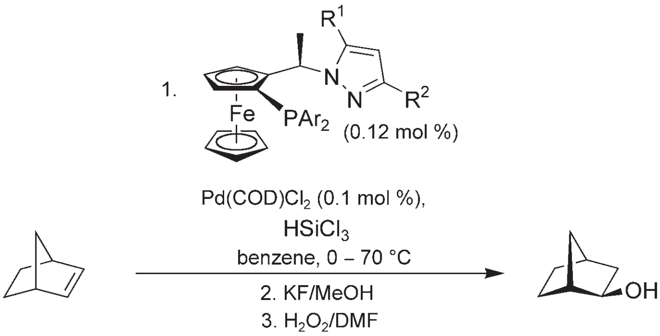
[a] Optical rotation indicated low *ee*.

Scheme 5. Sulfonated amines are good secondary donors.

Good activity was retained on returning to secondary nitrogen donors and to palladium complexes of ligands bearing *N*-methylsulfonyl or *N*-trifluoromethylsulfonyl groups (entries 5 to 8). Moreover, fine tuning for enantioselectivity of the donating properties of the nitrogen lone pair of the *N*-methylsulfonyl group (61% *ee*, entry 5) was achieved using a trifluoromethyl group **23** (72% *ee*, entry 7) or a sterically demanding side chain **24** (68% *ee*, entry 8). For the *N*-methylated sulfonamide **22** a dramatic reduction in selectivity was observed (7% *ee*, entry 6) and thus the presence of the hydrogen was seen as crucial to selectivity.

Further modifications of the chiral side chain of PPF-type ligands were reported by Togni and coworkers[15] who synthesised several pyrazole-containing ligands and examined their activity in AHS reactions (Scheme 6). Increasing the steric bulk of substituent R^2, which may be assumed to lower the co-ordinative power of the nitrogen, allowed the reaction to be operated at lower temperatures with a concomitant increase in selectivity (entries 1–3).

Reducing the electron donating power of R^2 by replacing the 2,4-6-trimethoxyphenyl group with a 2,4,6-trimethylphenyl group gave a palladium complex that was significantly more selective (91% *ee*, entry 4), and lowering the co-ordinative ability of phosphorus by the introduction of electron-withdrawing 3,5-bis-(trifluoromethyl)phenyl groups gave a catalyst that delivered the highest enantioselectivity (99% *ee*, entry 5) recorded for this substrate to date.

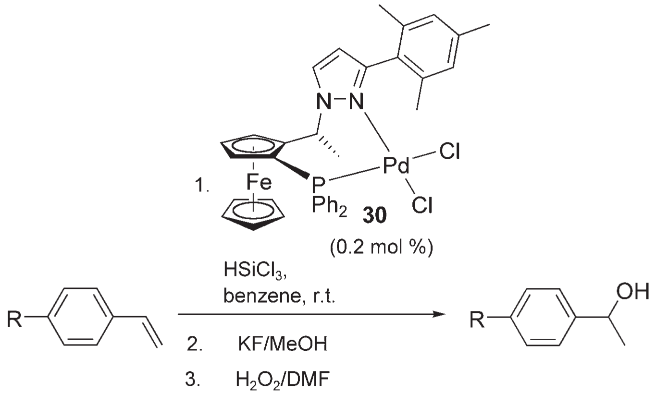


Entry	L	R^1	R^2	Ar	T [°C]	Yield [%]	*ee* [%]
1	**25**	Me	Me	Ph	70	54	10
2	**26**	Me	Ph	Ph	50	47	39
3	**27**	H	$2,4,6\text{-}(OMe)_3C_6H_2$	Ph	0	30	82
4	**28**	H	$2,4,6\text{-}(Me)_3C_6H_2$	Ph	0	56	91
5	**29**	H	$2,4,6\text{-}(Me)_3C_6H_2$	$3,5\text{-}(CF_3)_3C_6H_3$	0	59	99

Norbornene:$HSiCl_3$:$Pd(COD)Cl_2$:Ligand = 1:1.3:0.001:0.012. Reaction times not given. Yields refer to isolated alcohol.

Scheme 6. A pyrazole secondary donor delivers 99% *ee* for the AHS of norbornene.

The same researchers probed the relationship between the electronic nature of the substrate and stereoselectivity.[15] A series of *para*-substituted styrenes was subjected to AHS using catalyst **30**, the palladium complex of ligand **28** (Scheme 7). It was found that the electronic nature of the *para*-substituent plays a



R = NMe_2, 49% yield, 64% *ee* (*R*)

R = Cl, 61% yield, 67% *ee* (*S*)

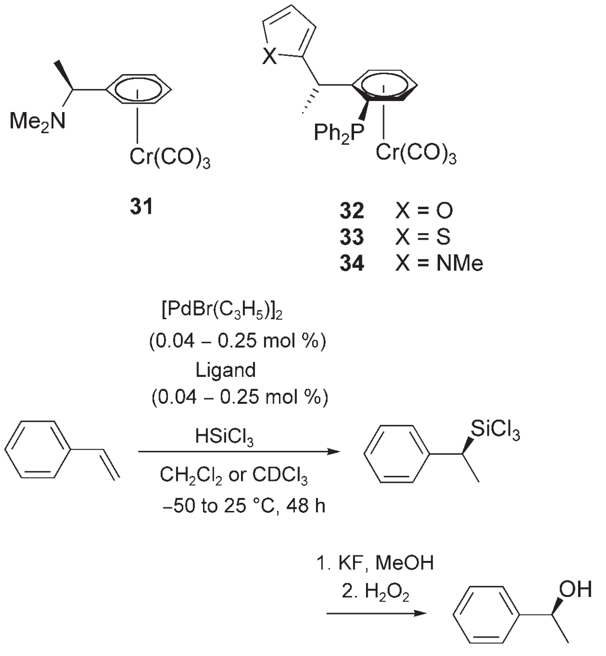
Scheme 7. Reversal of enantioselectivity by a remote substrate substituent.

crucial role in the sense of asymmetric induction. Electron-rich 4-dimethylaminostyrene gave the highest *R*-selectivity (64% *ee*) whereas 4-chlorostyrene afforded the *S*-product with 67% *ee.* The authors remarked that this was "a rare example of enantioselectivity reversal due to a remote substituent in the substrate". In any case, the result serves to underline the sensitivity of the reaction to steric and electronic influences of both ligand and substrate. A Hammett correlation study[15] revealed evidence for a build-up of positive charge in the transition state of the enantioselectivity-determining step of the catalytic cycle, which was regarded as evidence for η^3 co-ordination of the substrate.[16]

The tricarbonyl chromium complex of (*S*)-phenylethylamine **31** has served as a starting point for the synthesis of planar chiral chromium ligands,[17] just as Ugi's amine provides a gateway for ferrocene ligands. Ligands incorporating heterocyclic secondary donors were synthesised and applied to the AHS of styrenes (Scheme 8). A clear dependence of enantioselectivity on temperature was observed (entries 1 and 2), and both the furan **32** (87% *ee*, entry 2) and thiophene **33** (92% *ee*, entry 3) containing ligands delivered high levels of stereocontrol at −50 to −40 °C. The *N*-methylpyrrolyl ligand **34** was active at −50 °C but the enantioselectivity was lower (65% *ee*, entry 4).

Replacing the heterocyclic group of **32** with a methoxy group (Scheme 9), using a chiral base-mediated approach to arene(tricarbonyl)chromium complexes,[18] gave ligand **35** which required a higher catalyst loading (0.5 mol% *vs.* 0.04 mol%) to achieve approximately the same selectivity at ambient temperature as **32** (entry 1). This may reflect stronger ligand binding in **35** compared to **32**. Modification of the benzylic substituent to give ligands **36** and **37** led to improved enantioselectivity (entries 2 and 3), but the catalyst generated from ligand **37** proved to be inactive below ambient temperature (entry 4), supporting the hypothesis that the secondary donor interactions are stronger in **35**–**37** than in **32**–**34**.

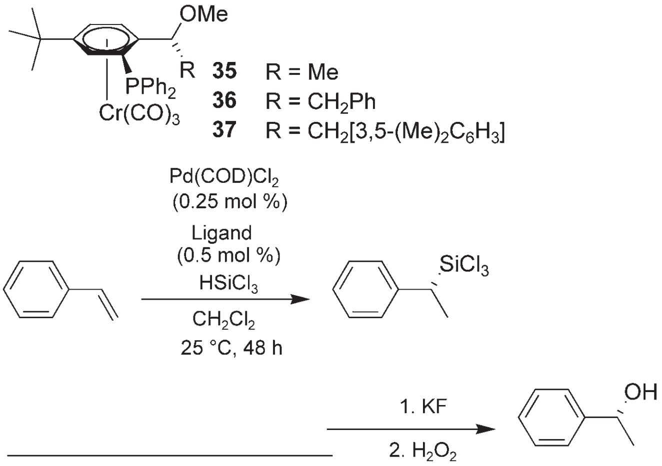
In a further study by Togni,[19] the structure of palladium complexes containing two $SiCl_3$ ligands was probed. Complex **30**, derived from ligand **28**, reacted with an excess of $HSiCl_3$ to give complex **38** (Scheme 10), which was found to display an extremely long palladium-phosphorus bond (from its X-ray crystallographic structure) as well as a deviation from ideal square planar geometry.



Entry	L	Loading (mol %)	T [°C]	*ee* [%]
1[a]	**32**	0.04	25	47 (*S*)
2[b]	**32**	0.25	–40	87 (*S*)
3[b]	**33**	0.25	–50	92 (*S*)
4[b]	**34**	0.05	–50	65 (*S*)

Styrene:Pd = 1:0.0004 – 0.0025, catalyst Pd:Ligand = 1:1, preformed *in situ* or used as admix with identical results. Yield: 85 – 90%.
[a] Reacted in the absence of solvent for 2 min.
[b] Reacted in CH_2Cl_2 or $CDCl_3$ for 48 h.

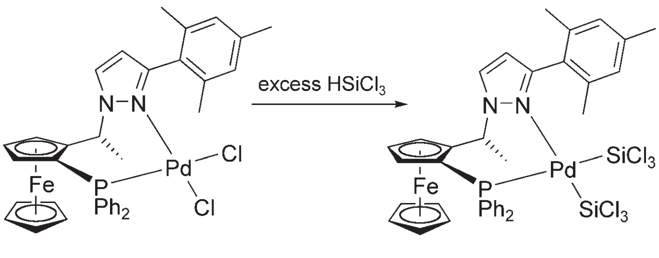
Scheme 8. Furan-, thiophene- and pyrrole-containing monophosphanes.



Entry	L	Yield [%]	*ee* [%]
1	**35**	95	46 (*R*)
2	**36**	93	55 (*R*)
3	**37**	91	73 (*R*)
4	**37**	0	-

Styrene:$HSiCl_3$:$Pd(COD)Cl_2$:Ligand = 1:1.5:0.0025:0.005.

Scheme 9. Ether substituents in arene tricarbonyl chromium based monophosphanes give active catalysts at ambient temperature but not below.



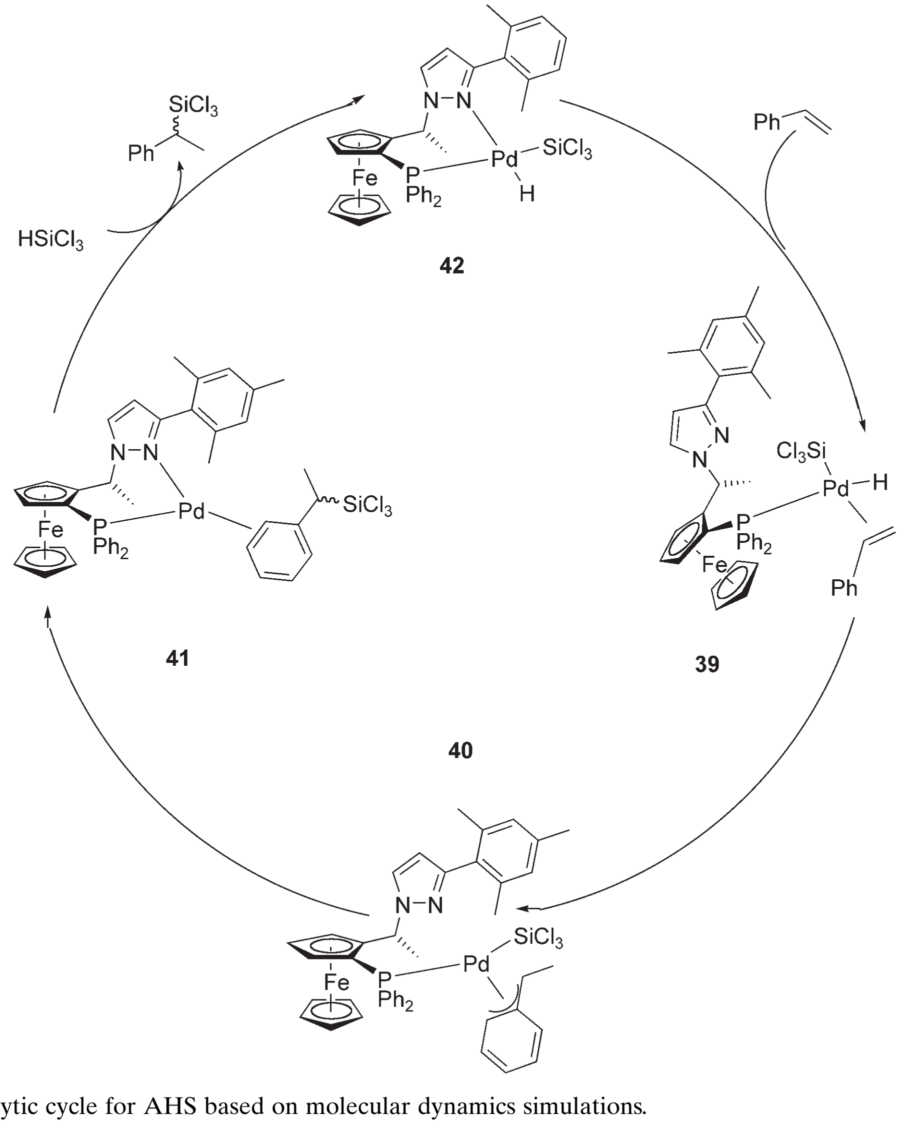
30 **38**

Scheme 10. Addition of $HSiCl_3$ to a key catalyst.

It was proposed that the lengthening of the Pd–P bond resulted from a combination of a strong *trans* effect of the $SiCl_3$ ligand enhanced by the presence of the phenyl groups on the phosphorus atom. The distortion from ideal square planar geometry was attributed to steric interactions between the trichlorosilyl ligands, the phenyl groups located on phosphorus and the bulky trimethylphenyl situated on the pyrazole fragment. The long bond and non-ideal geometry may imply a fluxionalitity that is favourable to AHS catalysis.

Togni and co-workers subsequently extended their investigation to look at the catalytic cycle for the AHS of styrene using a palladium complex of ligand **28**.[20] Hybrid QM/MM molecular dynamics simulations indicated that the catalytic cycle was initiated by the co-ordination of styrene (**39**, Scheme 11) with simultaneous pyrazole detachment. This is followed by insertion of the alkene into the palladium-hydride bond and the partial co-ordination of the arene to give the η^3 complex **40.**

Reductive elimination across the trichlorosilyl group and the benzylic carbon, accompanied by reattachment of the pyrazole, gave complex **41**. In the final step of the catalytic cycle, oxidative addition of



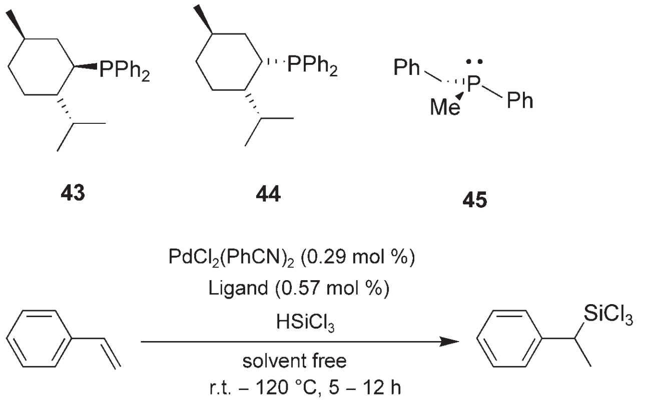
Scheme 11. A catalytic cycle for AHS based on molecular dynamics simulations.

$HSiCl_3$ and expulsion of the product regenerated the active catalyst **42**. The model is consistent with the importance of the role of secondary hemilabile donors in the AHS reaction.

To conclude this section, all the ligand systems examined above contain one aryl monophosphane moiety in combination with a heteroatomic (N, O or S) secondary donor. The importance of the second donor has been shown and it seems that, in general, as the co-ordinative power of the donor atoms decreases, lower reaction temperatures are feasible, often resulting in improved enantioselectivities.

3 Ligands without Secondary Donors

In one of the first reports of AHS chemistry,[21] Tamao and Kumada reported the employment of the terpene-derived ligands menthyldiphenylphosphane **43** and neomenthyldiphenylphosphane **44**. Both ligands were found to give palladium complexes active at room temperature, the AHS of styrene being complete in 5 h (Scheme 12, entries 1 and 2). Ligand **43** gave the product with 34% *ee* (entry 1) and ligand **44** generated an *ee* of 22% (entry 2). For comparison, phosphane **45** required high reaction temperatures to achieve similar activity, and the selectivity was very low (entry 3).



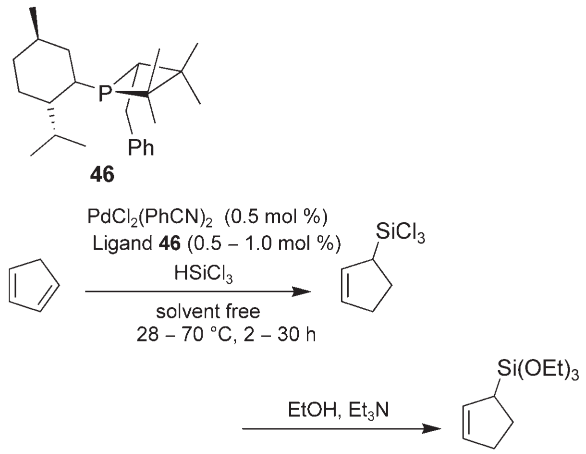
Entry	L	T [°C]	Time [h]	Yield [%]	*ee* [%]
1	**43**	r.t.	5	87	34 (*S*)
2	**44**	r.t.	5	87	22 (*R*)
3	**45**	120	12	70	2 (*R*)

Styrene:$HSiCl_3$:$PdCl_2(PhCN)_2$:Ligand = 1:2.95:0.0029:0.0057. The *ee* was determined by measurement of optical rotation of $SiMe_3$ derivatives.

Scheme 12. Monophosphanes without sites for secondary donation.

There are no obvious sites for secondary π- or σ-interactions between ligand and metal in these cases. The relatively low steric demand of ligand **45**, however, may facilitate the binding of a second equivalent of phosphane to palladium. The high reaction temperature required in this case (120 °C, entry 3) may thus reflect the amount of energy required to displace one phosphane in order for catalysis to proceed. In contrast, the increased steric bulk found in **43** and **44** inhibits the coordination of the second phosphane, thus allowing substrates to bind more readily and catalysis to proceed at lower temperatures.

In another early study, Marinetti and Ricard developed a palladium-catalysed hydrosilylation using phosphetanes as chiral ligands (Scheme 13).[22] The phosphetanes are noteworthy in that they are the only trialkylphosphanes to be used to date in the palladium-catalysed AHS of an olefinic substrate. During the course of this study, it was found that a catalyst preformed from one equivalent of phosphetane **46** (entry 1) was far more active than the catalyst preformed from two equivalents (entry 2) thus facilitating the use of lower reaction temperatures for AHS; in the case of cyclopentadiene, higher selectivity resulted (54% *vs.* 44% *ee*). Thus the presence of a



Entry	Pd:L	Time [h]	T [°C]	Yield [%]	*ee* [%]
1[a]	1:1	2	25 – 30	70	54 (*S*)
2[b]	1:2	30	70	26	44 (*S*)

Cyclopentadiene:$HSiCl_3$:catalyst = 1:1.1:0.005.

[a] The pre-catalyst was formed *in situ*.

[b] A preformed admix was employed. Both AHS reactions were quantitative and gave isolated yields of the product silane above 90% after being judged complete by NMR.

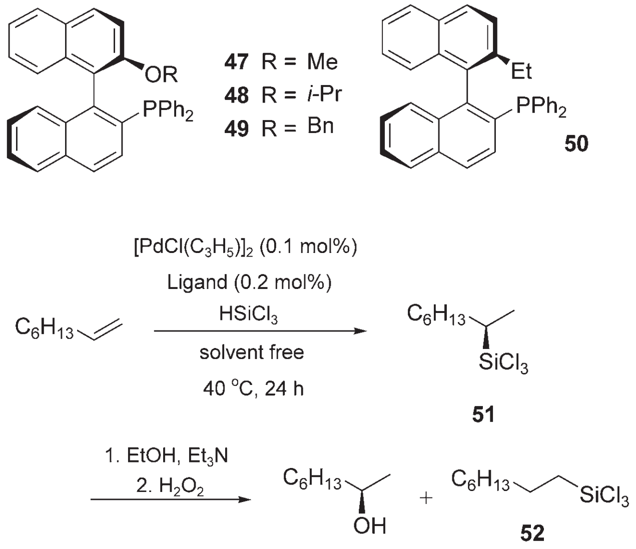
Scheme 13. A phosphetane ligand and the effect of varying the Pd:L ratio.

second equivalent of the relatively electron-rich trialkyl-monophosphane has a clear inhibitory effect on this AHS reaction.

4 Ligands with Less Well-Defined Secondary Donors

Perhaps the most successful chiral ligands across the whole field of asymmetric catalysis are those based on the binaphthyl skeleton. Monophosphane ligands with biaryl axial chirality were thus an obvious choice for AHS chemistry. In the first report on this subject[23] Hayashi and co-workers used the ligand MeO-MOP **47** and found that it gave good yields (>80%), regioselectivities (>9:1) and enantioselectivities (>94% *ee*) over a range of 1-alkenes. For the AHS of 1-octene, for example, ligand **47** delivered an 83% isolated yield of the desired secondary alcohol with 95% *ee* (Scheme 14, entry 1).

When the methoxy group of **47** was replaced with an isopropoxy group to give ligand **48**, a marginally lower *ee* was obtained using 1-octene as the substrate (91% *ee*, entry 2). Incorporation of a benzyloxy group, (ligand **49**), led to a catalyst that was found to be less efficient in terms of regioselectivity (80:20, entry 3), but with essentially the same activity and enantioselectivity as the catalyst derived from **47**. Substitution of the 2′ position with an ethyl group (ligand **50**) led to a catalyst of remarkably similar activity and selectivity to **47** (entry 4). These results certainly question the role of the oxygen atom in **47–49**, since in the case of **50** the second heteroatom is absent.

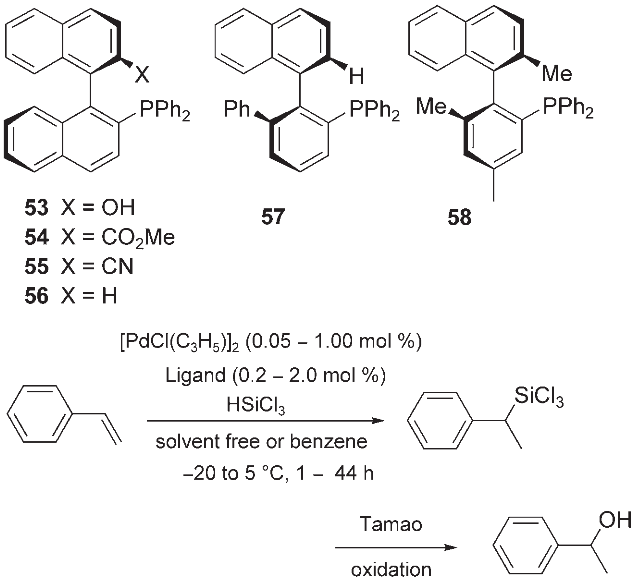


Entry	L	Yield [%][a]	**51**:**52**	*ee* [%]
1	**47**	83	93:7	95 (*R*)
2	**48**	88	90:10	91 (*R*)
3	**49**	85	80:20	95 (*R*)
4	**50**	80	90:10	93 (*R*)

1-Octene:HSiCl$_3$:PdCl(C$_3$H$_5$):Ligand = 1:1.2:0.001:0.002.

[a] Yield refers to isolated yield of **51** by distillation.

Scheme 14. Hydrosilylation of 1-octene using MOP ligands.



Entry	L	Time [h]	T [°C]	Yield [%]	*ee* [%]
1[a]	**47**	24	0	100	14 (*R*)
2[b]	**47**	44	5	100	71 (*R*)
3[a]	**50**	12	0	100	18 (*R*)
4[a]	**53**	22	0	84	34 (*S*)
5[a]	**54**	12	0	100	30 (*S*)
6[a]	**55**	24	0	100	26 (*R*)
7[a]	**56**	36	0	68	95 (*R*)
8[a]	**57**	24	0	85	91 (*R*)
9[a]	**58**	96	0	87	50 (*S*)
10[a]	**59**	1	0	93	97 (*S*)
11[a]	**59**	24	–20	85	98 (*S*)

Catalysts were prepared *in situ* in all cases.

Styrene:HSiCl$_3$:PdCl(C$_3$H$_5$):Ligand = 1:1.2:0.001:0.002.

[a] Reactions conducted in solvent free conditions.

[b] Conducted using benzene as solvent.

Scheme 15. Hydrosilylation of styrene using MOP and related ligands.

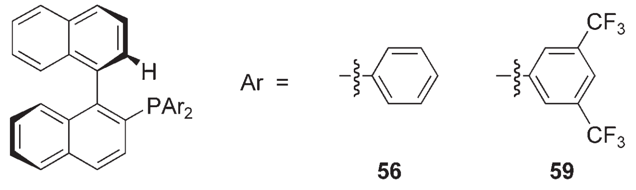


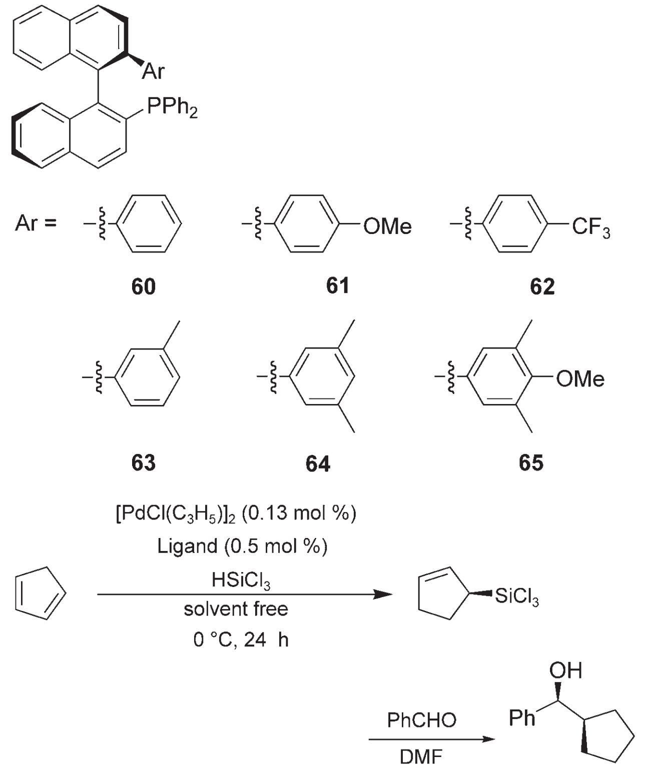
Figure 1. H-MOP, **56**,and an electron-deficient analogue **59**.

Later, ligands with other functional groups were required for substrates for which **47** did not perform well.[24] For example, in the AHS of styrene MeO-MOP gave a product of 14% *ee* (Scheme 15, entry 1), although the use of benzene as solvent did raise this to 71% *ee* (entry 2).[25] Ligands substituted with Et, OH, CO_2Me and CN (**50**, **53**, **54**, and **55**) gave no better than 34% *ee* (entries 3–6), suggesting that the electronic nature of the 2′ substituent did not play a decisive role in enantioselectivity. However, H-MOP **56**, which has minimal steric bulk in the 2′ position gave the product alcohol with excellent enantioselectivity (95% *ee*, entry 7).

Ligand **57**, like H-MOP, is sterically unencumbered in the 2' position and this monophosphane gave 91% *ee* under similar conditions (entry 8).[26] A related structure **58**, reported by Bringmann and co-workers,[27] with a methyl group in the 2′ position gave 50% *ee* for the same substrate under similar conditions (entry 9). All these results emphasised the important role the 2′ substituent plays in AHS chemistry, although the exact nature of the interactions remained unclear at this point.

The H-MOP structure was developed further by the Hayashi group in 2001[28] with their synthesis of the electron-deficient phosphane analogue **59** (Figure 1). Monophosphane **59** was found to be active at a lower temperature (−20°C) than H-MOP, **56**, giving the highest enantioselectivity (98% *ee*) reported for the AHS of styrene at the time (entry 11).

A series of Ar-MOP ligands (**60–65**) was also synthesised.[29] The results for AHS of cyclopentadiene (Scheme 16) show that as the aryl becomes more electron rich (**61**, entry 2), or more sterically demanding (**63** and **64**, entries 4 and 5), or both (**65**, entry 6), the enantioselectivity improves. The exact cause of these effects is unclear but one possibility is that the nature of the aryl group forces a particular geometry in the biaryl scaffold that affects the enantioselectivity of the catalyst. Alternatively, the aryl group may be interacting with the palladium during the catalytic cycle (see later). It is reasonable to expect that as the aryl becomes more electron rich, interactions with palladium would become more significant.



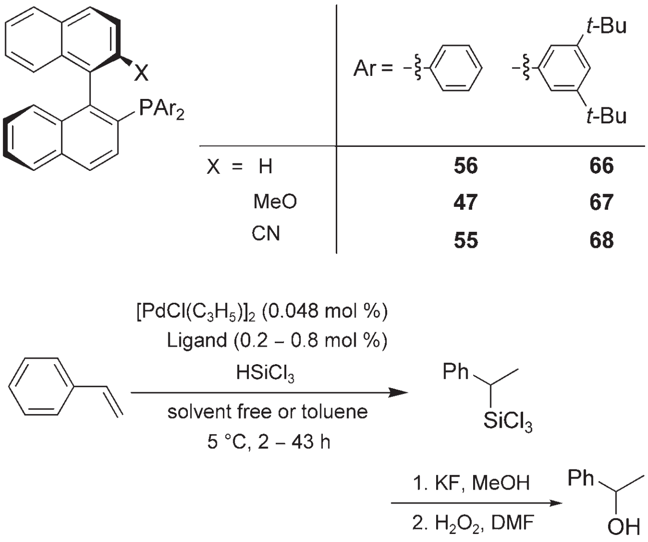
Entry	L	Yield [%]	*ee* [%]
1	**60**	84	69 (*S*)
2	**61**	84	76 (*S*)
3	**62**	83	47 (*S*)
4	**63**	85	76 (*S*)
5	**64**	83	79 (*S*)
6	**65**	79	88 (*S*)

Diene:$HSiCl_3$:Pd:L = 1:1.2:0.0025:0.0050.
Reactions carried out in the absence of solvent.

Scheme 16. Hydrosilylation of cyclopentadiene using Ar-MOP ligands.

Pregosin and co-workers[30] developed a series of MOP ligands previously used by the Hayashi group[25] by adding steric bulk around the aryls on phosphorus. For the AHS of styrene a slight drop off in *ee* was recorded for H-MOP when using the more sterically demanding analogue **66** (92% *vs.* 88%, Scheme 17, entries 1 and 2). However, the use of 3,5-di-*tert*-butylphenyl groups (**67** and **68**) gave up to 50% improvement in enantioselectivity for MeO-MOP (57% *ee*, entry 4) and CN-MOP (82% *ee*, entry 6), over their unsubstituted analogues (entries 3 and 5). A change of product enantiomer was noted on going from (H-MOP) or (MeO-MOP) ligands (entries 1–4) to (CN-MOP) ligands (entries 5 and 6). The authors proposed that restricted rotation of the P−C_{ipso} bond may be significant in creating a rigid chiral pocket, an effect that they had already observed in bisphosphane ligated catalysis.[31]

Hayashi recognised the key role of monophosphanes in AHS chemistry when he noted that palladi-



Entry	L	Time [h]	Yield [%]	*ee* [%]
1	**56**	20	100	92 (*R*)
2	**66**	16	100	88 (*R*)
3	**47**	16	100	7 (*R*)
4	**67**	43	100	57 (*R*)
5	**55**	2	100	42 (*S*)
6	**68**	2	100	81 (*S*)

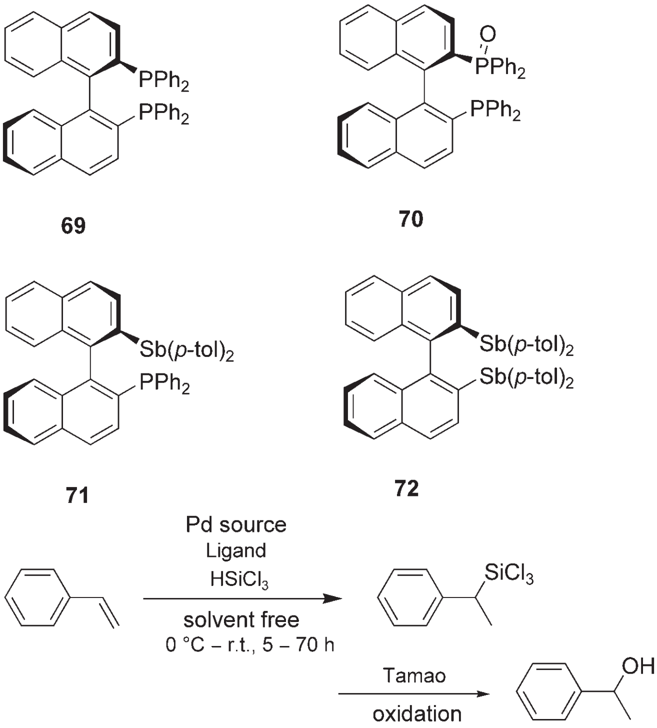
Styrene:$HSiCl_3$:$[PdCl(C_3H_5)]_2$:Ligand = 1:1.24:0.00048:0.0019.

Scheme 17. The effect of adding sterically demanding groups to MOP ligands.

um complexes co-ordinated with chelating bisphosphane ligands such as BINAP **69** did not catalyse the AHS of 1-hexene at temperatures as high as 80 °C.[23] Hayashi proposed that the presence of two strongly co-ordinating donors creates a palladium species that disfavours the binding of substrates and retards the catalytic cycle.

Oxidation of one of the diphenylphosphino groups in BINAP to a diphenylphosphine oxide moiety gives the ligand BINAPO, **70**, the coordinative ability of which is modulated to such an extent that AHS catalysis proceeds readily at room temperature. The AHS of styrene using BINAPO was carried out by Gladiali and co-workers[32] who noted low asymmetric induction (18% *ee*, Scheme 18, entry 1) under solvent free conditions. However, employing benzene as a solvent gave a much improved result with the enantioselectivity rising to 72% (entry 2). These two results are remarkably similar to those obtained with Hayashi's MeO-MOP ligand **47** (see Scheme 15, entries 1 and 2).

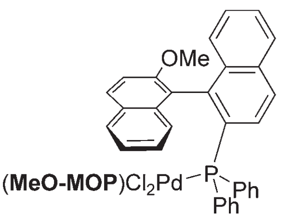
Recently, Fujihara and Tamura reported the synthesis of BINAP-stabilised palladium nanoparticles of particularly small size (diameter <2 nm).[33] In contrast to previous findings for palladium-BINAP complexes, it was found that the AHS of styrene took place using the nanoparticles at ambient temperature and below. At room temperature in the absence of solvent an 81% yield of (*S*)-phenylethanol was obtained with 75% *ee* (entry 3). At 0 °C the catalyst retained activity and the enantioselectivity rose to an impressive 95% *ee* (entry 4). The exact nature of the



Entry	L	Pd source	Pd:L [mol %]	T [°C]	Time [h]	Yield [%]	*ee* [%]
1[a,d,e]	**70**	$[Pd(allyl)Cl]_2$	0.1:0.2	r.t.	70	100	18 (*S*)
2[a,d,f]	**70**	$[Pd(allyl)Cl]_2$	0.1:0.2	r.t.	70	100	72 (*S*)
3[b,d,e,g]	**69**	nanoparticles	n/a	r.t.	5	81	75 (*S*)
4[b,e,h]	**69**	nanoparticles	n/a	0	5	n/a	95 (*S*)
5[c,e]	**71**	$[Pd(allyl)Cl]_2$	0.1:0.2	0	10	78	95 (*R*)
6[c,e]	**72**	$[Pd(allyl)Cl]_2$	0.1:0.2	0	24	10	12 (*R*)

[a] Styrene:$HSiCl_3$:$[PdCl(C_3H_5)]_2$:Ligand = 1:1.2:0.0005:0.001.
[b] Styrene:$HSiCl_3$ = 1:1.
[c] Styrene:$HSiCl_3$:$[PdCl(C_3H_5)]_2$:Ligand = 1:1.2:0.0005:0.002.
[d] Yield of 1-trichlorosilyl-1-phenylethane.
[e] Reaction conducted in solvent free conditions.
[f] Reaction conducted in benzene.
[g] 53 mg of catalyst used.
[h] Amount of catalyst not given.

Scheme 18. AHS of styrene using BINAP and derivatives.

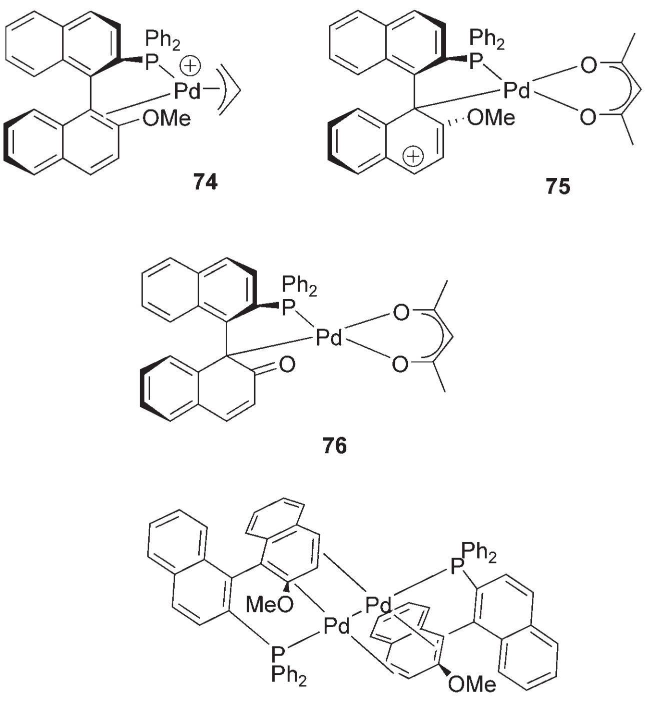


73

Figure 2. The structure of a palladium complex of MeO-MOP.

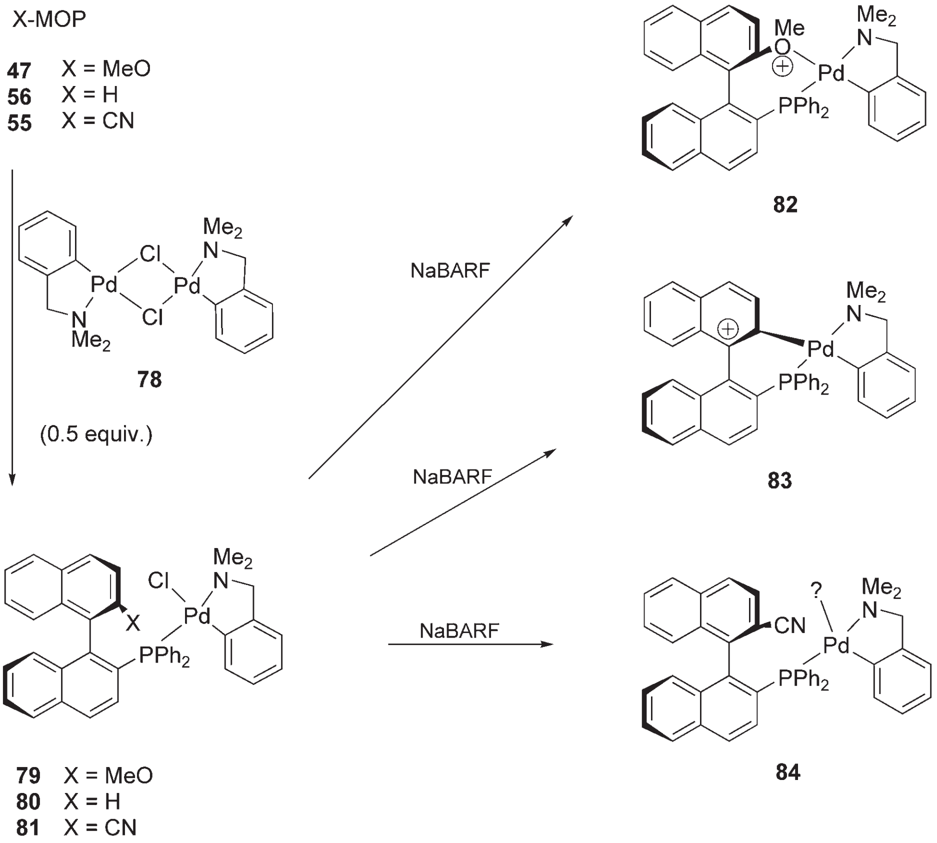
active catalyst was not discussed by the authors, but the reaction was conducted under solvent-free conditions and no obvious source of donation to palladium, other than BINAP, was present. It is thus unclear at present why the behaviour of the palladium-BINAP nanoparticles differs from that of molecular palladium-BINAP.

In 2004 Kurita and co-workers reported the synthesis and application of BINAPSb **71**.[34] This ligand was applied to the AHS of styrene and gave the product 1-phenylethanol in good yield (78%) and enantioselectivity (95%) over 10 h at 0°C (entry 5), a result that the authors noted was similar to that obtained with H-MOP (Scheme 15, entry 7). The bis-stibano ligand BINASb **72** was much less active, giving 10%



74 **75** **76** **77**

Figure 3. An insight into the rich coordination chemistry of MeO-MOP.



47 X = MeO
56 X = H
55 X = CN

78

79 X = MeO
80 X = H
81 X = CN

82 **83** **84**

Scheme 19. A range of interactions occur between biaryl ligands and palladium.

yield and 12% *ee* over 24 h under the same reaction conditions (entry 6).

In order to try to explain the activities and selectivities observed using biaryl-monophosphanes, Hayashi obtained an *X*-ray structure of a $PdCl_2$ derivative of MeO-MOP in 1995 (**73**).[35] This revealed that the methoxy group was directed away from the metal in a position where interaction would be difficult (Figure 2). Although it can be seen how this type of co-ordination may create an effective chiral environment, it seems likely that other, less effective, MOP ligands would be capable of adopting similar orientations. It is difficult to correlate this (solid state) finding with the large differences seen between the performances of different MOP ligands (in solution).

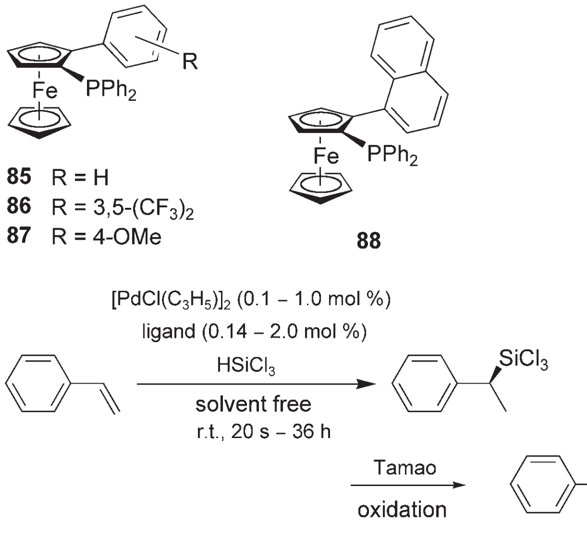
Despite the excellent results obtained in the AHS using Pd-MOP complexes, it is only quite recently that the co-ordination chemistry of this class of molecules has been probed. Novel structures such as **74**,[36] **75**,[37] **76**,[37] and **77**[38] (Figure 3) have emerged that offer new insight into the binding modes that can operate in these ligand systems. For example, P,C bidentate ligands were found in **75** and **76**, whilst partial co-ordination of the methoxyarene occurs in **74** and **77**.

The nature of secondary interactions between palladium and MOP ligands were further probed in a series of experiments relevant to AHS chemistry.[38]

Reactions of MeO-MOP, H-MOP and CN-MOP with the palladium dimer **78** (Scheme 19) gave three palladium chloride complexes **79**, **80** and **81** in which the X groups showed no evidence for interactions with palladium (in agreement with the findings of Hayashi). Subsequent chloride abstraction using NaBARF gave complex **82** in which a σ-bond is observed between palladium and the methoxy group, complex **83**, in which a weak Pd–C σ-bond from the naphthyl backbone was proposed based on ^{13}C NMR data, and complex **84**, which presented an uncertain picture with no visible π- or σ-complexation. However, from the data available, the authors did not believe the palladium species to be tri-coordinate.

These results show that several modes of binding are available to MOP ligands and shed new light on why it has proven possible to fine tune this ligand family to give high enantioselectivities across a range of substrates. It also serves to underline how secondary interactions need to be considered in AHS chemistry.

Ligands where a π-system could be involved in a secondary interaction to palladium include the planar chiral ferrocene-based ligands of Johannsen and coworkers. In a preliminary communication[39] the authors reported that the use of ligand **85** in the AHS of styrene led to good selectivity (76% *ee*, Scheme 20, entry 1). In a later report it was found that increasing the electron density of the aromatic ring was beneficial to reactivity in AHS,[40] but poor activity and selectivity were observed for ligand **86** containing *meta*-trifluoromethyl groups (entry 2). Ligand **87**, with a methoxy group in the *para* position of the attached aromatic ring, gave optimal results in terms of selectivity (86% *ee*, entry 3).



85 R = H
86 R = 3,5-$(CF_3)_2$
87 R = 4-OMe

88

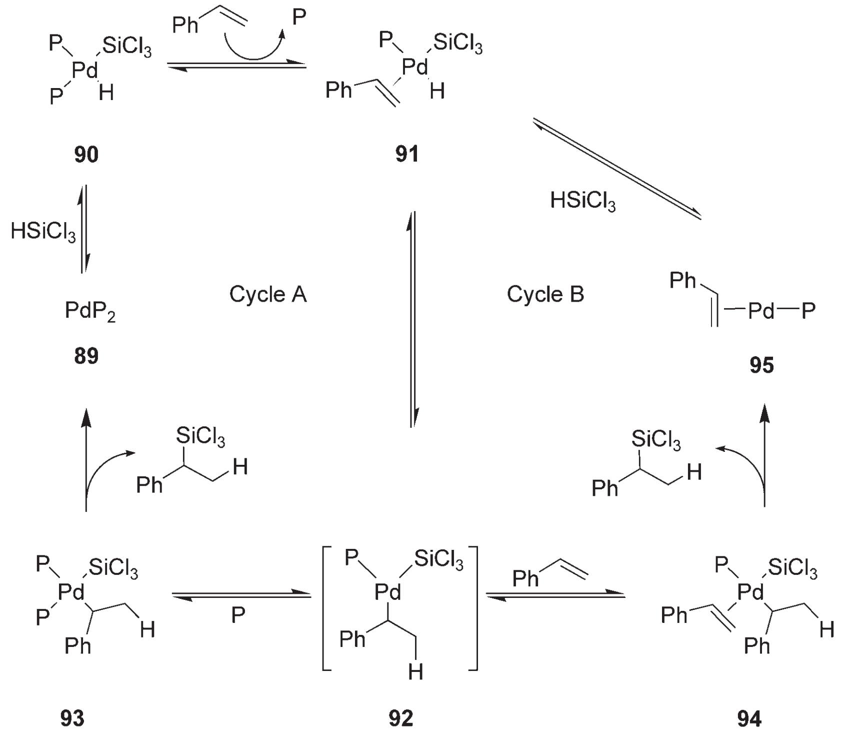
Entry	L	Pd [mol %]	Ligand [mol %]	Time	*ee* (%)
1	**85**	1	2	1.5 h	76 (*S*)
2	**86**	1	2	8 h	25 (*S*)
3	**87**	1	2	1.6 h	86 (*S*)
4	**88**	1	2	1.5 h	79 (*S*)
5	**88**	0.1	0.2	3.5 h	85 (*S*)
6	**88**	0.1	0.16	5 min	63 (*S*)
7	**88**	0.1	0.14	20 s	69 (*S*)
8	**88**	0.1	0.12	20 s	62 (*S*)

Styrene:$HSiCl_3$ = 1:1.2. All reactions conducted at room temperature in the absence of solvent and stopped upon completion (100% conversion).

Scheme 20. Aryl ferrocene ligands and a dramatic effect from varying the metal to ligand ratio.

Ligand **88**, which bears some structural similarity to H-MOP **56**, was found to be a good ligand in terms of enantioselectivity under similar conditions (up to 85% *ee*, using a 1:2 palladium to ligand ratio, entries 4 and 5). However, an impressive rate enhancement was observed upon lowering the relative amount of ligand to metal (entries 6–8). When using a palladium to ligand ratio of between 0.1:0.12–0.14 the reaction proceeded so fast that it was judged complete after just 20 s (entries 7 and 8), equivalent to a turnover frequency of 180,000 per hour.

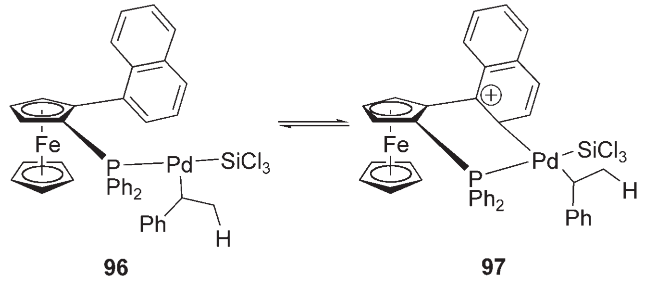
The authors stated that a catalytic system employing a 1:2 metal-ligand ratio would utilise the second equivalent of phosphane to stabilise palladium,[40] and they proposed that two catalytic cycles could be in op-



Scheme 21. Proposed catalytic cycle for higher loadings of phosphane (cycle A) and lower loading of phosphane (cycle B).

eration depending on the relative amount of phosphane present (Scheme 21). In cycle A oxidative addition of trichlorosilane to PdP_2, **89**, gives a 16-electron species **90** still coordinated to two equivalents of phosphane. Ligand exchange of a phosphane for styrene to give **91** must then occur for catalysis to proceed. This is not expected to be a facile process due to the high affinity of phosphane ligands for palladium. Migratory insertion follows to give **92** which is subsequently stabilised by reco-ordination of the second phosphane to give **93**. In the final step the product is formed by reductive elimination and PdP_2 is reformed. At lower concentrations of phosphane, the authors proposed that it is styrene that stabilises the transient three co-ordinate species **92** to give **94** (Cycle B). The product is generated by reductive elimination which gives the two co-ordinate species **95**. The cycle is then continued by the oxidative addition of trichlorosilane to regenerate **91**. Cycle B would be expected to proceed faster than cycle A, since it does not require the displacement of a phosphane at any point and this could explain the dramatic rate enhancement observed at lower ligand to metal ratios.

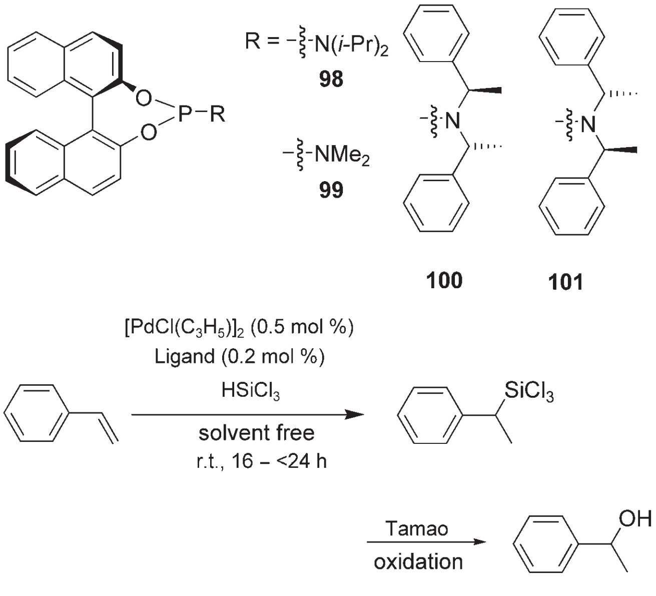
From the studies of Pregosin and co-workers described above, it seems possible that the stabilisation of intermediates in the cycle operating at lower phosphane concentrations may arise not from the co-ordination of styrene, but by interactions with the adjacent arene ring on the ferrocene, e.g., the pseudo-biarylic skeleton of **88** could stabilise a species such as **96** to give species **97** (Scheme 22).



Scheme 22. Stabilisation may come not from styrene but from the naphthyl group.

Finally, chiral phosphoramidites **98–101**, originally introduced by Feringa for copper-catalysed enantioselective addition of dialkyl zinc reagents to enones,[41] were reported, by Johannsen and co-workers,[42] to be very active in catalysing the AHS of styrenes (Scheme 23, entries 1–4). The amine substituents determined selectivity with achiral side chains (ligands **98** and **99**) giving moderate asymmetric induction (69% and 20% *ee*, entries 1 and 2), whilst ligand **100** proved to be extremely effective giving the product with an impressive 99% *ee* (entry 3).

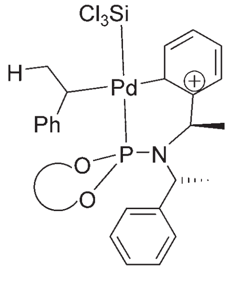
Diastereomeric ligand **101** retained the activity of **100** but the selectivity dropped off (60% *ee*, entry 4) and the opposite enantiomer was obtained. Excellent enantioselectivities were also reported across a range



Entry	L	Time [h]	Conversion	*ee* [%]
1	**98**	<24	100	55 (*S*)
2	**99**	<24	100	20 (*R*)
3	**100**	16	100	99 (*R*)
4	**101**	<24	100	60 (*S*)

Styrene:HSiCl$_3$:[PdCl(C$_3$H$_5$)]$_2$:Ligand = 1:1.2:0.005:0.

Scheme 23. AHS using chiral phosphoramidites.



102

Figure 4. Do benzyl groups act as secondary donors in phosphoramidite based catalysis?

of substituted styrenes. Clearly the chiral side chains in ligands **98–101** play a dominant role in enantioselection in this reaction, perhaps indicating that a secondary interaction may occur between palladium and their benzyl groups as illustrated by the resonance-stabilised chelate **102** (Figure 4).[43]

5 Conclusions

Potential secondary donation is an important factor to consider when designing a successful monophosphane ligand for a palladium-catalysed AHS as it may have a significant impact on catalyst activity and selectivity. In the ferrocenyl-type systems discussed in Section 2, the secondary donor needs to be strong enough to compete with the co-ordination of a second equivalent of monophosphane, but weak enough to allow facile co-ordination of reactants. The more active catalysts that result from ligands which have been optimised for this characteristic operate at lower temperatures and generally lead to improved enantioselectivities. For ligands based on the biaryl skeleton, the importance of secondary interactions is less clear, but pioneering studies on palladium complexes of MeO-MOP suggest that secondary interactions may provide an explanation for the experimentally observed differences in activity and selectivity displayed by members of the biaryl-monophosphane family. Further studies of this nature are awaited.

References

[1] For example, see: I. Ojima (Ed.), *Catalytic Asymmetric Synthesis*. Wiley-VCH, New York, **2000**.

[2] a) G. R. Jones, Y. Landais, *Tetrahedron* **1996**, *52*, 7599–7662; b) K. Tamao, T. Kakui, M. Kumada, *J. Am. Chem. Soc.* **1978**, *100*, 2268–2269; c) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics* **1983**, *2*, 1694–1696.

[3] W. S. Knowles, M. J. Sabacky, *Chem. Commun.* **1968**, 1445–1446.

[4] L. Horner, H. Siegel, H. Buthe, *Angew. Chem. Int. Ed.* **1968**, *7*, 942–942.

[5] *Comprehensive Asymmetric Catalysis*, Vols. 1–3 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Berlin, **1999**.

[6] T. Hayashi, *Acc. Chem. Res.* **2000**, *33*, 354–362.

[7] For reviews on the AHS see a) T. Hiyama, T. Kusumoto, in: *Comprehensive Organic Synthesis*, Vol. 8, (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp 120–131; b) T. Hayashi, in: *Comprehensive Asymmetric Catalysis*, Vol. 1, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Berlin, **1999**, pp. 319–333; c) H. Nishiyama, K. Ito, in: *Catalytic Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, pp 111–132; d) J. Tang, T. Hayashi, in: *Catalytic Heterofunctionalisation*, (Eds.: A. Togni, H. Grutzmacher), Wiley-VCH, New York, **2001**, pp 73–90; e) L. Tietze, H. Ito, H. P. Bell, *Chem. Rev.* **2004**, *104*, 3453–3516.

[8] T. P. Yoon, E. N. Jacobson, *Science* **2003**, *299*, 1691–1693.

[9] T. Hayashi, K. Tamao, Y. Katsuro, I. Nakae, M. Kumada, *Tetrahedron Lett.* **1980**, *21*, 1871–1874.

[10] D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389–5393.

[11] T. Hayashi, Y. Matsumoto, I. Morikawa, Y. Ito, *Tetrahedron: Asymmetry* **1990**, *1*, 151–154.

[12] H. Ohmura, H. Matsuhashi, M. Tanaka, M. Kuroboshi, T. Hiyama, Y. Hatanaka, K. Goda, *J. Organomet. Chem.* **1995**, *499*, 167–171.

[13] J. W. Han, N. Tokunaga, T. Hayashi, *Helv. Chim. Acta* **2002**, *85*, 3848–3854.

[14] a) T. Okada, T. Morimoto, K. Achiwa, *Chem. Lett.* **1990**, 999–1002; b) S. Sakuraba, T. Okada, T. Morimoto, K. Achiwa, *Chem. Pharm. Bull.* **1995**, *43*, 927–934.

[15] G. Pioda, A. Togni, *Tetrahedron: Asymmetry* **1998**, *9*, 3903–3910.

[16] For a related hydrocyanation study on styrenes, see: A. L. Casalnuovo, T. V. Rajanbabu, T. A. Ayers, T. H. Warren, *J. Am. Chem. Soc.* **1994**, *116*, 9869–9882.

[17] I. Weber, G. B. Jones, *Tetrahedron Lett.* **2001**, *42*, 6983–6986.

[18] S. E. Gibson, J. T. Rendell, M. Rudd, *Synthesis* **2006**, 3631–3638.

[19] T. K. Woo, G. Pioda, U. Rothlisberger, A. Togni, *Organometallics* **2000**, *19*, 2144–2152.

[20] a) A. Magistrato, T. K. Woo, A. Togni, U. Rothlisberger, *Organometallics* **2004**, *23*, 3218–3227; b) A. Magistrato, A. Togni, U. Rothlisberger, *Organometallics* **2006**, *25*, 1151–1157.

[21] Y. Kiso, K. Yamamoto, K. Tamao, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4373–4374; Y. Kiso, K. Yamamoto, K. Tamao, M. Kumada *J. Organomet. Chem.* **1981**, *210*, 9–17.

[22] A. Marinetti, *Tetrahedron Lett.* **1994**, *35*, 5861–5864; A. Marinetti, L. Ricard, *Organometallics* **1994**, *13*, 3956–3962.

[23] Y. Uozumi, T. Hayashi, *J. Am. Chem. Soc.* **1991**, *113*, 9887–9888.

[24] Y. Uozumi, K. Kitayama, T. Hayashi, *Tetrahedron: Asymmetry* **1993**, *4*, 2419–2422.

[25] K. Kitayama, Y. Uozumi, T. Hayashi, *J. Chem. Soc., Chem. Commun.* **1995**, 1533–1534.

[26] T. Hayashi, S. Niizuma, T. Kamikawa, N. Suzuki, Y. Uozumi, *J. Am. Chem. Soc.* **1995**, *117*, 9101–9102.

[27] G. Bringmann, A. Wuzik, M. Breuning, P. Henschel, K. Peters, E.-M. Peters, *Tetrahedron: Asymmetry* **1999**, *10*, 3025–3031.

[28] T. Hayashi, S. Hirate, K. Kitayama, H. Tsuji, A. Torii, Y. Uozumi, *J. Org. Chem.* **2001**, *66*, 1441–1449.

[29] T. Hayashi, J. W. Han, A. Takeda, J. Tang, K. Nohumi, K. Mukaide, H. Tsuji, Y. Uozumi. *Adv. Synth. Catal.* **2001**, *343*, 279–283.

[30] P. Dotta, P. G. A. Kumar, P. S. Pregosin, A. Albinati, S. Rizzato, *Organometallics* **2004**, *23*, 2295–2304.

[31] For example, see: M. Tschoerner, P. Pregosin, A. Albinati, *Organometallics* **1999**, *18*, 670–678.

[32] S. Gladiali, S. Pulacchini, D. Fabbri, M. Manassero, M. Sansoni, *Tetrahedron: Asymmetry* **1998**, *9*, 391–395.

[33] M. Tamura, H. Fujihara, *J. Am. Chem. Soc.* **2003**, *125*, 15742–15743.

[34] S. Yasuike, S. Kawara, S. Okajima, H. Seki, K. Yamaguchi, J. Kurita, *Tetrahedron Lett.* **2004**, *45*, 9135–9138.

[35] Y. Uozumi, K. Kitayama, T. Hayashi, K. Yanagi, E. Fukuyo, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 713–722.

[36] a) P. Kocovsky, S. Vykocil, I. Cisarova, J. Sejbal, I. Tislerova, M. Smrcina, G. C. Lloyd-Jones, S. C. Stephen, C. P. Butts, M. Murray, M. Langer, *J. Am. Chem. Soc.* **1999**, *121*, 7714–7715; b) G. C. Lloyd-Jones, S. C. Stephen, M. Murray, C. P. Butts, S. Vyskocil, P. Kocovsky, *Chem. Eur. J.* **2000**, *6*, 4348–4357.

[37] P. Dotta, P. G. A. Kumar, P. S. Pregosin, A. Albinati, S. Rizzato, *Organometallics* **2003**, *22*, 5345–5349.

[38] P. Dotta, P. G. A. Kumar, P. S. Pregosin, A. Albinati, S. Rizzato, *Organometallics* **2004**, *23*, 4247–4254.

[39] H. L. Pedersen, M. Johannsen, *Chem. Commun.* **1999**, 2517–2518.

[40] H. L. Pedersen, M. Johannsen, *J. Org. Chem.* **2002**, *67*, 7982–7994.

[41] For example, see: a) A. H. M. de Vries, A. Meetsma, B. L. Feringa, *Angew. Chem. Int. Ed.* **1996**, *35*, 2375–2376.

[42] J. F. Jensen, B. Y. Svendsen, T. V. la Cour, H. L. Pedersen, M. Johannsen, *J. Am. Chem. Soc.* **2002**, *124*, 4558–4559.

[43] It is of note in this context, however, that the methyl groups of the Feringa ligands undergo C-H activation in iridium-catalysed reactions: A. Leitner, S. Shekhar, M. J. Pouy, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 15506–15514.