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Nickel (II) Complexes Bearing Phosphinoaryl Oxazoline Ligands as Pro-catalysts for Grignard Cross-coupling

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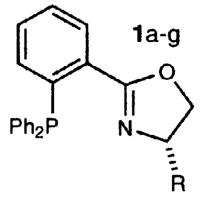
Abstract: Ni(II) complexes bearing chiral phosphinoaryl oxazoline ligands are pro-catalysts for cross-coupling of Z-styryl bromide with 1-phenethyl magnesium chloride. Under suitable conditions, there is a dynamic kinetic resolution resulting in moderate enantioselectivity. The nature of the substituent at the stereogenic centre of the oxazoline ligand affects catalysis in two distinct ways: smaller substituents lead to improved rates and selectivities whilst polar substituents reverse the sense of asymmetric induction. The solid state structure of one phosphinoaryl oxazoline Ni(II) pro-catalyst was determined by single crystal x-ray diffraction. © 1997 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

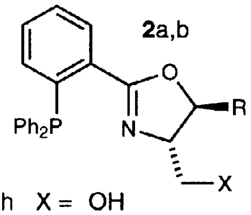
Since their simultaneous and independent introduction[1] by *Pfaltz*, *Helmchen* and *Williams* in 1993, there has been growing interest in the application of phosphinoaryl oxazoline ligands[2] e.g. **1**, **2**, **3** to asymmetric catalysis.

1a-g



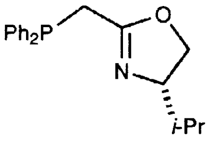
1a R = Me
1b *i*-Pr
1c *i*-Bu
1d Bn
1e *t*-Bu
1f Ph
1g *p*-$CH_2C_6H_4$-OH

2a,b



2a R = Ph X = OH
2b H NMe_2

3



The spectacular results reported for Pd-catalysed allylic alkylation[3] of 1,3-diphenylpropenyl systems were also realised in the addition of nitrogen nucleophiles.[4] More recently, exceedingly high enantiomeric excesses (ee's) have been achieved by double stereodifferentiation with nitromethane as nucleophile.[5] Furthermore, the methodology has been extended to non-symmetrical diaryl alkyl propenyl systems,[6] and intramolecular cyclisations[7] as well as to the use of sulphonate[8] and α-imino phosphonate[9] nucleophiles. Pd-phosphinoaryl oxazoline complexes also catalyse highly regio- and enantio-selective Heck-type reactions[10] as well as enantioselective copolymerisation processes.[11] Other metal complexes bearing phosphinoaryl oxazoline ligands have also proved to be useful as asymmetric catalysts, thus W(0) complexes catalyse the enantio- and regio-selective addition of dimethyl malonate to non-symmetrical cinnamyl type allylic systems,[12] Ru(II) complexes

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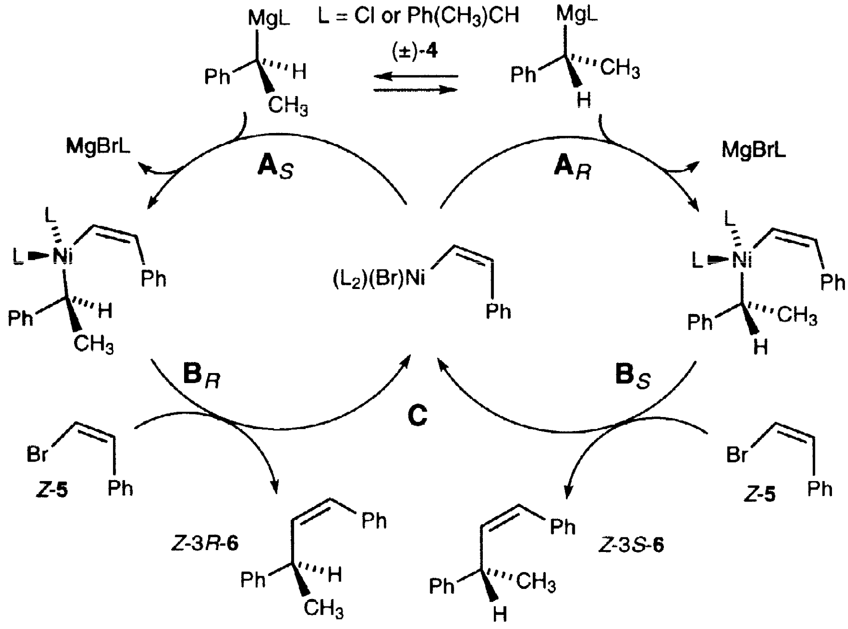
catalyse transfer hydrogenation of dialkyl ketones,[13] Rh(I) complexes catalyse the hydrosilylation of ketones[14] and Ir(I) complexes catalyse the hydrogenation of imines and alkenes.[15]

A variety of Pd or Ni catalysts bearing chiral diphosphine and, in particular, amino-phosphine ligands have been employed for enantioselective Grignard cross-coupling.[16] We therefore set out to examine whether the diphenylphosphino oxazoline ligands **1**a-g, **2**a-b and **3** would be useful for this reaction class. Whilst this work was in progress, Richards *et al.* reported on the synthesis and application of ferrocenyl phosphinoaryl oxazoline ligands to a variety of catalysed reactions, including Pd-catalysed Grignard cross-coupling.[17]

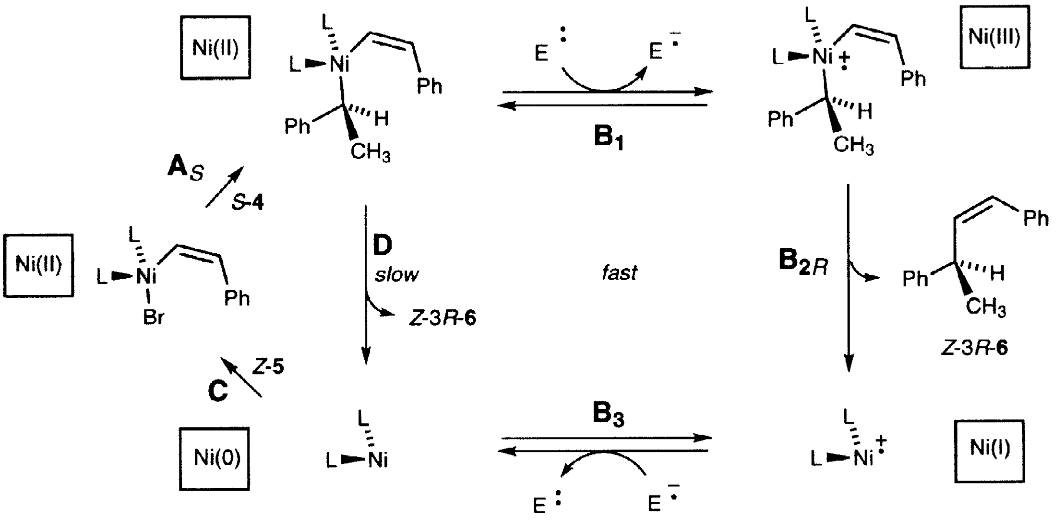
A conventional mechanism[18] for one type of enantioselective Ni-catalysed Grignard cross coupling is shown in Scheme 1.



Scheme 1 - A simplistic mechanism for a dynamic kinetic resolution of 1-phenethyl magnesium chloride (±)-**4** *via* Ni-catalysed cross-coupling with Z-β-bromostyrene **5**. Monomer-dimer equilibria etc. of racemizing (±)-**4** have been omitted for clarity.

Grignard reagent (±)-**4** stereomutates (racemizes) spontaneously. If this occurs faster than the rate of the cross-coupling reaction, then the process can become a dynamic kinetic resolution. Under these conditions, the chemical yield of one enantiomer of product, e.g. Z-**6**, could approach 100% provided that perfect diastereoselectivity is maintained throughout the catalytic cycle. There is little known about the intimate mechanistic details of enantioselective Grignard cross-coupling. Certainly, diastereoselectivity may arise at either or both of steps **A** and **B** (scheme 1) since transmetallation may be reversible. Furthermore, little or nothing is known about whether the transmetallated Ni(II) species is able to epimerise, although there is no obvious mechanism by which it may do so. Grignard reagent (±)-**4** may racemize *via* the Schlenk equilibrium and thus the transmetallating step (step **A**, scheme 1) could involve either or both the alkyl magnesium chloride (*R*/*S*) and the dialkyl magnesium (*R*/*S* + *meso*) equilibrium partners[18b] or their halide bridged dimers or adducts. In addition, whilst *cis* reductive elimination from Ni(II) dialkyl species is known to occur, it is slow relative to the rates usually observed under the catalytic cross-coupling conditions. Electron transfer agents (E, scheme 2) e.g. O_2, sp^2 halides and Grignard reagents are known to accelerate Ni-catalysed cross-coupling. It has been proposed that the overall catalytic cycle involves not just a simple redox shuttle between formal oxidation states (0) and (II) but that reductive elimination (step $\mathbf{B}_{2R}$, scheme 2) is induced by SET Ni(II) ->

Ni(III) (scheme 2, step **B$_1$**). After reductive elimination a reverse direction SET (Ni(I) -> Ni(0) (scheme 2, step **B$_3$**) completes the cycle.



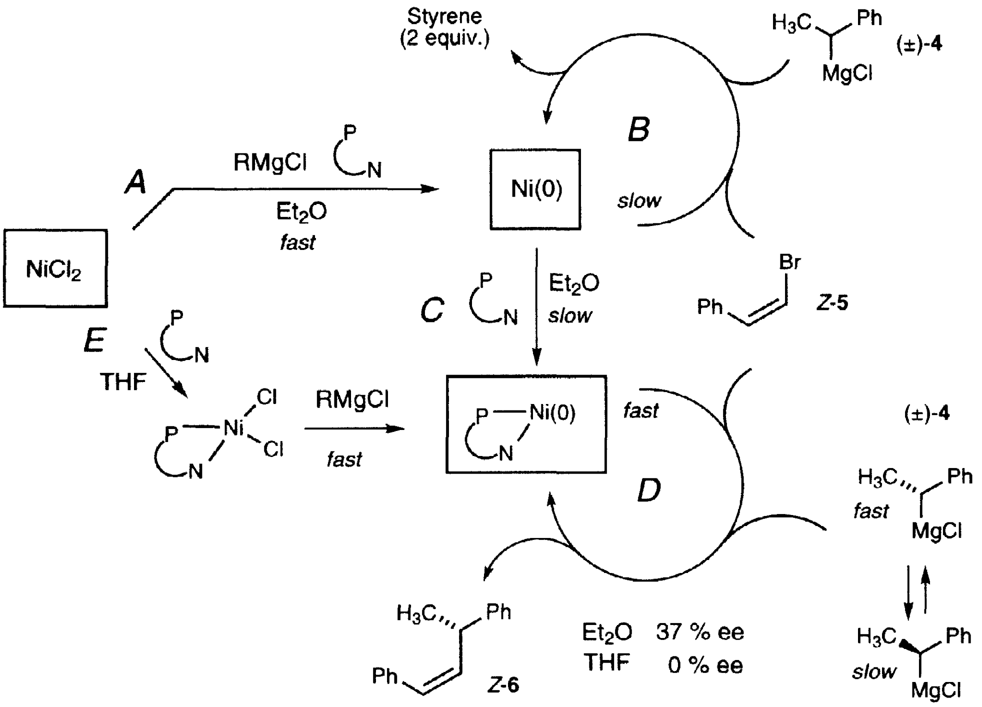
Scheme 2 - Two possible catalytic cycles leading to, for example, Z-3-*R*-**6**. Alternative pathways **B** and **D** regenerate a Ni(0) species. Pathways analogous to **B** have been postulated to account for the large rate accelerations induced in Ni-catalysed cross-couplings by the presence of an electron transfer agents (E).[18] "E" may be molecular oxygen, halide substrate or Grignard reagent. Whilst pathways analogous to **D** are precedented stoichiometrically, the rate is usually considered to be non-competitive with **B**.

RESULTS

We chose to study the Ni-catalysed reaction of 1-phenethyl magnesium chloride (±)-**4** with *E*- and *Z*-β-bromostyrenes *E*-**5** and *Z*-**5** to give the cross coupling products *E*- and *Z*-1,3-diphenylbutenes *E*-**6** and *Z*-**6**. *E*-β-Bromostyrene *E*-**5** was prepared by purification of commercial material (15% *Z*-**5**) (elimination with *i*-PrONa) and *Z*-β-bromostyrene *Z*-**5** by bromination of cinnamic acid followed by anhydrous debromodecarboxylation. The isomeric purity of both *E*-**5** and *Z*-**5** was estimated to be ≥ 99.8 % by GC and NMR. Dry-stir activation of Mg-turnings, as reported by Brown *et al.*,[19] was found to be essential for the preparation of high purity ethereal solutions of 1-phenethyl magnesium chloride (±)-**4**.

Samples of pure racemic *E*- and *Z*-**6** were prepared by separation of the products of a Wittig reaction of benzyl bromide with (±)-2-phenylpropionaldehyde. After many attempts, chiral GC resolved the enantiomers of *Z*-**6** (but not *E*-**6**), though this method required long run-times (> 2h.). Surprisingly, despite the lack of polar functionality, the enantiomers of both *E*- and *Z*-**6** were cleanly and efficiently separable using chiral HPLC. Furthermore, the run-times (15 - 25 min) made the HPLC method highly convenient.

In initial experiments on the cross coupling reaction, we followed the general method of Kumada *et al.* for couplings catalysed by Ni complexes of various amino-ferrocenyl phosphines.[20] Thus a mixture of $NiCl_2$, ligand **1c** and *Z*-β-bromostyrene *Z*-**5** (1:3:67) in Et_2O was frozen, treated with an excess 1-phenethyl magnesium chloride (±)-**4** (1.3 equiv.) as a solution in Et_2O and then warmed to 25 °C (pathway *A*, scheme 3). Under these conditions, the insoluble yellow $NiCl_2$ was rapidly reduced to afford a green solution and catalysis ensued. The turnover rate was poor (≤ 50 turnovers per hour) and the enantioselectivity low (≤ 20 % ee). Other ligands, **1b,e,f** gave worse results and in all cases there were low yields of the desired *Z*-**6** (≤40 %) with the bulk of the reaction product being styrene. Although $NiCl_2$ on its own is not a pro-catalyst for cross-coupling, under these conditions there is significant Ni-catalysed hydrodebromination of *E*-β-bromostyrene *via* β-H transfer[21] from 1-phenethyl magnesium chloride (±)-**4** (pathway ***B***, scheme 3). Hence, in contrast to amino-ferrocenyl phosphines, the phosphinoaryl oxazoline ligands **1b,c,e,f** coordinate the *in situ* prepared Ni(0) species relatively slowly (pathway ***C***, scheme 3).



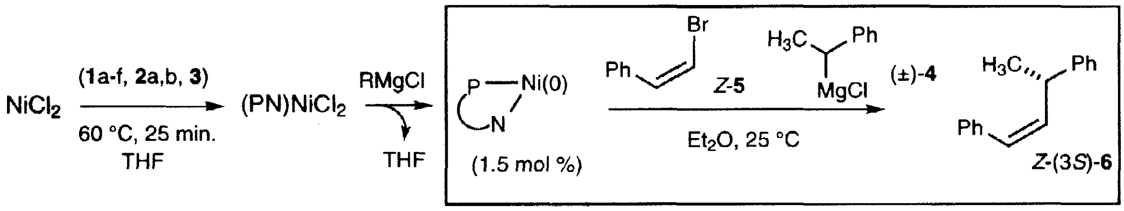
Scheme 3 - the dramatic effect of the solvent and method of catalyst generation on the course of the Ni-catalysed cross-coupling of *Z*-β-bromostyrene *Z*-**5** with 1-phenethyl magnesium chloride (±)-**4**. Phosphinoaryl oxazoline ligand is represented by (P—N)

Despite many attempts, $NiCl_2$ could not be reacted with ligands **1a-f** in Et_2O to form detectable complexes of the type [(**1a-f**)$NiCl_2$]. However, on switching from Et_2O to THF, a pinky-red colouration occurred on the surface of the bright-yellow insoluble $NiCl_2$. The reaction could be driven to completion by heating to 60 °C for 25 min. to afford a deep red-purple homogenous solution (pathway ***E***, scheme 3).

When a deep red-purple THF solution of [(**1c**)$NiCl_2$] was employed as a catalyst (1.5 mol %) for cross coupling of *Z*-**5** in THF by addition of (±)-**4** (1.3 equiv.) in Et_2O, *Z*-**6** was obtained in reasonable yield (69%) but was racemic (pathway ***D***, scheme 3). The lack of enantioselectivity is possibly due to a change in aggregate equilibria and racemization rates of (±)-**4** upon changing to the more solvating THF. The use of pure Et_2O appeared necessary for enantioselectivity and accordingly, when the THF was rigorously removed *in vacuo* from the *in situ* prepared complex [(**1c**)$NiCl_2$] prior to addition of the Et_2O, the reaction afforded *Z*-**6** with 37 % ee (pathway ***D***, scheme 3). Notably, the reaction was complete within 3 min. (≥ 1340 turnovers per h.) and styrene was not detected as a side-product. The cross-coupling product *Z*-**6** (37 % ee) was isolated and subjected to Ru-catalysed oxidative double bond cleavage. As described by Sharpless, this reaction proceeds without racemisation of α-stereocentres.[22] The resultant 2-phenylpropanoic acid was esterified with TMS-diazomethane[23] to afford methyl 2-phenylpropanoate which was determined to be 37 % ee 2-(*R*) by chiral GC with (±) and ≥99 % ee samples as standards.[24] Consequently, the stereochemistry of *Z*-**6** could be assigned as

Z-3*S*-1,3-diphenylbutene. A series of complexes [(**1**a-g)NiCl$_2$] prepared *in situ* in THF were examined as catalysts for the cross-coupling under the THF-free conditions - Table 1.

Table 1 - Rates (tph), enantioselectivities and yields for the dynamic kinetic resolution[a] of 1-phenethyl magnesium chloride (±)-**4** *via* cross coupling with *Z*-β-bromostyrene *Z*-**5** in the presence of 1.5 mol % of nickel complexes [(**1a**-g)NiCl$_2$], [(**2a**-b)NiCl$_2$], or [(**3**)NiCl$_2$]. The pro-catalysts [(**1a**-g, **2a**-b or **3**)NiCl$_2$] were prepared *in situ* by complexation of NiCl$_2$ (1.5 mol %) with ligands **1**,**2** or **3** (4.5 mol%) in THF followed by removal of THF *in vacuo* then reaction in Et$_2$O.



Entry	ligand	4- substituent[b]	tph[c] / 10^3.	ee (%)[d]	product
1	**1a**	Me	2.0	38	*Z*-3*S*
2	**1b**	*i*-Pr	0.8	26	*Z*-3*S*
3	**1c**	*i*-Bu	1.3	37	*Z*-3*S*
4	**1d**	Bn	≥ 0.8	41	*Z*-3*S*
5	**1e**	*t*-Bu	0.1	10	*Z*-3*S*
6	**1f**	Ph	≥ 0.4	19	*Z*-3*S*
7	**1g**	*p*-CH$_2$C$_6$H$_4$-OH	0.2	32	*Z*-3*S*
8	**2a**	CH$_2$OH	0.2	41	*Z*-3*R*
9	**2b**	CH$_2$NMe$_2$	≥ 0.4	13	*Z*-3*R*
10	**3**	*i*-Pr	0.005	0	-

a: typical conditions [Ni] = 0.75 mM (1.5 mol%), [ligand] = 2.25 mM, [*Z*-**5**] = 50 mM, [(±)-**4**] = 125 mM. b: The substituent at the stereogenic 4- position on the oxazoline ring of ligands **1**a-f, **2**a,b or **3**. c: The rate as catalyst turnovers per hour (tph) was estimated by TLC sampling at 1, 5 or 15 min. intervals. d: The enantiomeric excess (ee) of the cross coupling product *Z*-1,3-diphenylbutene *Z*-**6** was measured by chiral HPLC (Chiralcel OD).

Notably, ligands **2a** (entry 8) and **2b** (entry 9) gave products of the opposite configuration - Table 1- whilst ligand **3**, bearing an alkyl linkage from phosphine to oxazoline (instead of aryl) gave a catalyst of low activity and no enantioselectivity (entry 10).

In the series of complexes [(**1**)NiCl$_2$] prepared from **1**a-f an unexpected dependence of the rate and enantioselectivity on the steric volume of the oxazoline substituent at the stereogenic centre (Me, *i*-Bu, *i*-Pr, Ph or *t*-Bu) was noted (entries 1-3, 5, 6). Whilst these rates are necessarily approximate, a clear trend emerges: the smaller the stereogenic substituent, the faster the rate (tph) and the higher the enantioselectivity (Fig. 1).

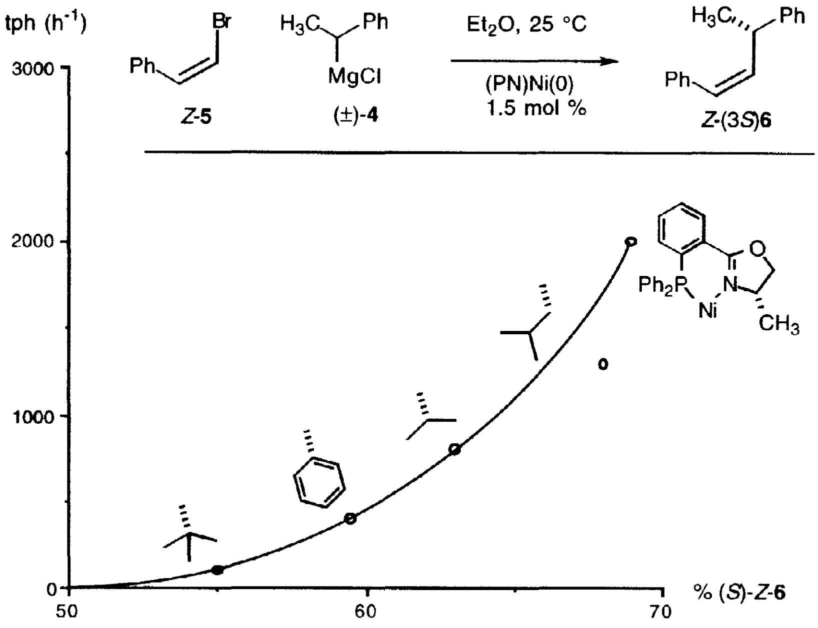
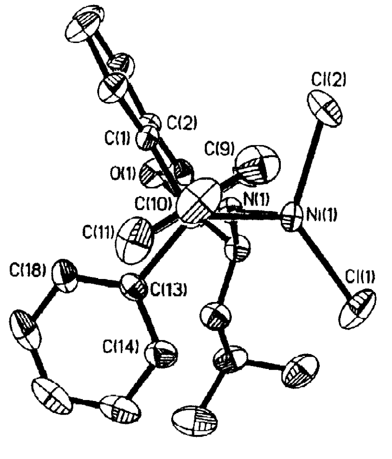


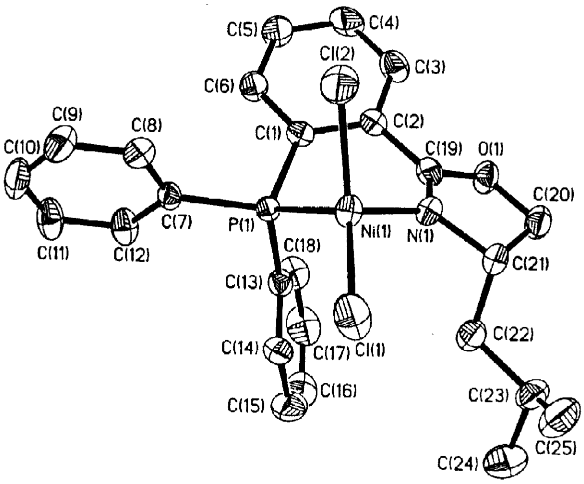
Figure 1. Relationship between rate as catalysts turnovers per hour (tph) and enantioselectivity (% (*S*)-*Z*-**6**) for the dynamic kinetic resolution of 1-phenethyl magnesium chloride (±)-**4** *via* cross coupling with *Z*-β-bromostyrene *Z*-**5** in the presence of 1.5 mol % of nickel complexes [(**1**a-c,e,f)NiCl$_2$] in Et$_2$O at 25 °C. Typical conditions [Ni] = 0.75 mM (1.5 mol%), [ligand] = 2.25 mM, [*Z*-**5**] = 50 mM, [(±)-**4**] = 125 mM. The rate (tph) was calculated from the time for complete substrate consumption (67 turnovers) as estimated by TLC samples taken at 1 minute intervals. The enantiomeric excess (ee) of the cross coupling product *Z*-1,3-diphenylbutene *Z*-**6** was measured by chiral HPLC (Chiralcel OD).

Since the complex [(**1c**)NiCl$_2$] generated *in situ* from ligand **1c** and NiCl$_2$ was amongst the most selective of the catalyst precursors, we attempted to isolate and characterise it. Slow diffusion of *t*-BuOMe into a concentrated THF solution of [(1c)NiCl$_2$] afforded the complex as large deep-purple to black cubes (52 % yield from NiCl$_2$).

CDCl$_3$, CD$_2$Cl$_2$ and d$_8$-THF solutions of [(1c)NiCl$_2$] are an intense red-purple colour and display paramagnetic contact shifts and broadening in their ^{1}H, ^{13}C and ^{31}P NMR spectra. Interestingly, red-purple coloured solutions of [(1c)NiCl$_2$] in THF became orange and then bright yellow on cooling to -78 °C. The ^{1}H NMR spectrum in d$_8$-THF showed the onset of significant broadening between -30 and -40 °C - at which temperature the solution is orange in colour. On further cooling, the resonances sharpened again. At -82 °C, the solution was bright yellow, but the chemical shift range (-10 to +25 ppm) indicated that the complex was still paramagnetic. The change in colour is consistent with loose coordination of the THF resulting in a second, yellow coloured high-spin complex as the temperature is reduced to -82 °C. However, is seems likely that only one THF is coordinated since a low spin Jahn-Teller distorted form is not observed. At intermediate temperatures, exchange of THF occurs at the NMR time-scale and an orange (red + yellow) colour is observed. Consistent with this explanation, CH$_2$Cl$_2$ and CDCl$_3$ solutions remained pinky-purple even on cooling to their freezing points.

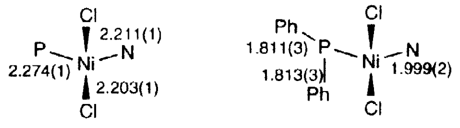
The solid-state structure of [(1c)NiCl$_2$] was determined by single crystal X-ray diffraction. The structure comprises a slightly distorted tetrahedral Ni(II) centre (d^8 - high spin), with no unusual bond-lengths or angles. Two views (P-Ni-N plane) together with atomic coordinates and selected lengths / angles are given in Fig 2.



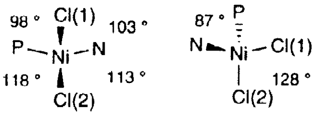


atom	x	y	z	U(eq)
Ni(1)	3239(1)	7931(1)	1208(1)	26(1)
P(1)	3546(1)	9538(1)	1760(1)	21(1)
O(1)	7043(2)	9694(2)	645(1)	34(1)
N(1)	4835(3)	8795(2)	815(1)	25(1)
Cl(1)	1086(1)	7770(1)	820(1)	54(1)
Cl(2)	4475(1)	6414(1)	1603(1)	46(1)
C(1)	5554(3)	9495(2)	1875(1)	24(1)
C(2)	6584(3)	9330(2)	1489(1)	25(1)
C(3)	8097(4)	9252(3)	1584(1)	36(1)
C(4)	8624(4)	9330(3)	2059(1)	42(1)
C(5)	7626(4)	9492(3)	2441(1)	39(1)
C(6)	6112(4)	9580(3)	2346(1)	31(1)
C(7)	2642(3)	9513(3)	2351(1)	26(1)
C(8)	2335(4)	8325(3)	2563(1)	36(1)
C(9)	1588(5)	8268(3)	3005(1)	46(1)
C(10)	1143(4)	9378(4)	3235(1)	45(1)
C(11)	1452(4)	10563(3)	3029(1)	45(1)
C(12)	2207(4)	10634(3)	2587(1)	35(1)
C(13)	3195(4)	11111(2)	1503(1)	27(1)
C(14)	1853(4)	11310(3)	1261(1)	34(1)
C(15)	1539(5)	12485(3)	1048(1)	48(1)
C(16)	2594(5)	13470(3)	1076(1)	52(1)
C(17)	3930(5)	13273(3)	1312(1)	51(1)
C(18)	4243(4)	12102(3)	1524(1)	36(1)
C(19)	6076(3)	9239(2)	975(1)	26(1)
C(20)	6396(4)	9381(3)	168(1)	38(1)
C(21)	4770(3)	9038(3)	281(1)	29(1)
C(22)	3655(4)	10122(3)	180(1)	36(1)
C(23)	3288(4)	10321(3)	-360(1)	41(1)
C(24)	2454(6)	11594(4)	-424(2)	68(1)
C(25)	2369(5)	9206(4)	-563(1)	54(1)

Selected Bond Lengths



Selected Bond Angles



Aryl Ring Positions relative to P-Ni-N plane

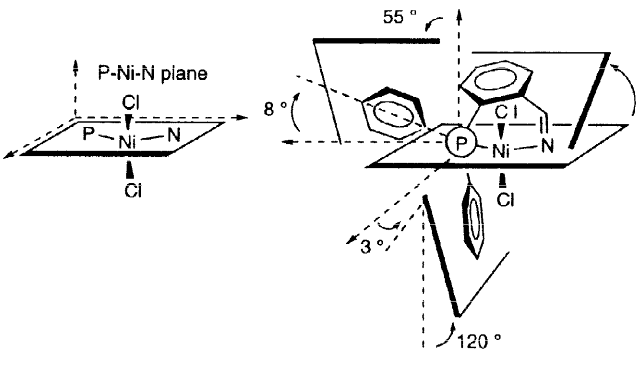
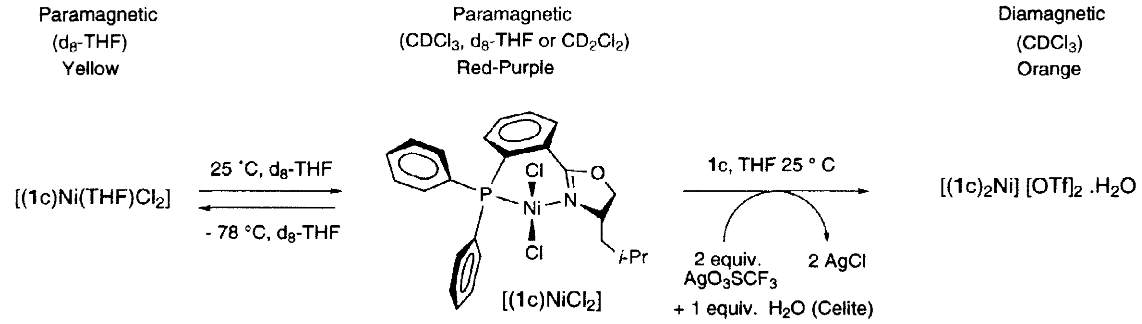


Figure 2. The single crystal x-ray structure of (**1c**)NiCl$_2$ together with atomic coordinates (x 10^4), equivalent isotropic displacement parameters (Å^2 x 10^3) and selected bond angles(deg) and lengths (Å). $C_{24}H_{17}Cl_2NiOP$; crystal system: orthorhombic; space group P2(1)2(1)2(1); Cell dimensions: a 8.9223(12) b 10.416(2) c 27.453(3); V = 2551.4(6) Å^3; F(000) = 1265; λ = 0.71073; crystal size 0.7 x 0.50 x 0.46 mm; μ = 1.308 mm^{-1}; $\rho_{(calc)}$ = 1.614 Mgm^{-3}; T = 173(2) K; 5001 unique reflections, of which 0 suppressed [R(int) = 0.0312, R_σ = 0.0307]; Refinement method: full-matrix least-squares on F^2; final R indices: R_1 = 0.0327; R indices (all data): R_1 = 0.0372; Flack x parameter = -0.0067; largest difference peak and hole: 0.360 and -0.396 e.Å^3

Analogous complexes of the type [(**1**)$NiCl_2$] formed *in situ* from ligands **1e** and **1f** in THF were also a deep red-purple colour in solution and again reversibly became yellow on cooling. Attempts to crystallise these complexes led to the precipitation of amorphous yellow powders which re-dissolved in THF or CH_2Cl_2 to give deep purple-red solutions. Clearly, various factors influence the geometric and coordination number preferences of complexes of the type [(**1**)$NiCl_2$] and the stability of the d^8, tetrahedral high spin form (deep purple, paramagnetic) is similar to that of the five (or six) coordinate, high spin, yellow form. Furthermore, the equilibrium is easily and rapidly pushed in either direction by influence of solvent, temperature, crystal packing forces or subtle ligand steric effects, e.g. *i*-Bu versus *t*-Bu.

Based on the observation that the *iso*-Bu oxazoline complex [(**1c**)$NiCl_2$] maintains its deep red-purple colour on dissolution in THF at 25 °C and that paramagnetic NMR spectra are obtained, *vida supra*, it is assumed that it maintains some similarity in solution to its non-solvated solid-state structure. On addition of one equivalent of ligand **1c** and two equivalents of AgOTf the red-purple colour of a THF solution of [(**1c**)$NiCl_2$] was rapidly discharged and a bright orange solution obtained. After removal of AgCl by filtration through Celite, a complex of stoicheiometry [(**1c**)$_2$Ni][OTf]$_2$·H_2O was isolated in 97 % yield as orange blocks (Scheme 4). Presumably the water molecule is picked up from the Celite.

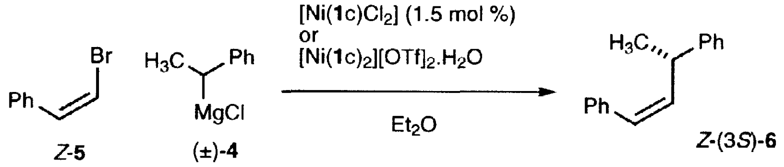


Scheme 4 - Representation of the solid state structure of [(**1c**)$NiCl_2$], which is assumed to persist in THF solution at 25 °C, and its reactions to produce [(**1c**)Ni(THF)Cl_2] and [(**1c**)$_2$Ni][OTf]$_2$·H_2O.

There was no evidence for a paramagnetic contact-shift in the solution phase NMR of this complex ($CDCl_3$). Presumably, in $CDCl_3$ solution [(**1c**)$_2$Ni][OTf]$_2$·H_2O is pseudo-squre planar or a Jahn-Teller distorted octahedron with loosely bound solvent, water molecule(s) or triflate counter ions at the octahedral vertices. The *trans* effect suggests that the P centres in [(**1c**)$_2$Ni][OTf]$_2$·H_2O will be mutually *cis*.[25]

Both of the analytically pure isolated complexes [(**1c**)$NiCl_2$] and [(**1c**)$_2$Ni][OTf]$_2$·H_2O were tested as pro-catalysts (1.5 mol %) for the cross-coupling reaction and the results are summarised in Table 2. Compared to the complex prepared *in situ* (as in Table 1), pure [(**1c**)$NiCl_2$] gave slightly higher enantioselectivity (41 % ee, Table 2, entry 1) with ca. ten-fold the turnover rate ($\geq 12 \times 10^3$ tph). Presence of ligand in excess of 1:1 stoicheiometry to Ni (addition of ligand **1c** to [(**1c**)$NiCl_2$] entry 2; or use of [(**1c**)$_2$Ni][OTf]$_2$·H_2O entry 3) reduced the rate and enantioselectivity.[26] Changing the solvent from Et_2O to THF (entry 4) or benzene (entry 5) afforded essentially racemic products - confirming the earlier conclusion that Et_2O is required for enantioselectivity. Use of lower temperature (-20 °C, entry 6) improved enantioselectivity somewhat (45 % ee) however at -78 °C (entry 7) there was no observable reaction over several hours. Slow addition of the substrate (entry 8), slow addition of Grignard (entry 9) and lower catalyst loading (0.05 mol %, entry 10) all led to reduced selectivities. Finally, use of *E*-β-bromostyrene *E*-**5** was not advantageous, leading to lowered enantioselectivity (entry 11).

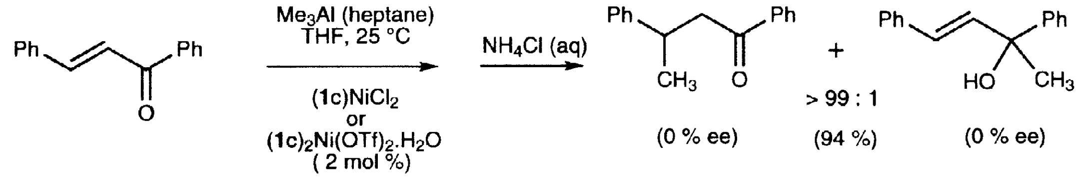
Table 2 - Rates (tph), enantioselectivities and yields for the dynamic kinetic resolution[a] of 1-phenethyl magnesium chloride (±)-**4** *via* cross coupling with *Z*-β-bromostyrene *Z*-**5** catalysed by nickel complexes [(1c)NiCl$_2$] or [(1c)$_2$Ni][OTf]$_2$·H$_2$O.



Entry	Complex	solvent, temp	tph / 10^3	ee (%)	yield (%)[b] *Z*-3*S*-**6**
1	[(1c)NiCl$_2$]	Et$_2$O, 25 °C	≥ 12	41	89 %
2	[(1c)NiCl$_2$] + (1c)[c]	Et$_2$O, 25 °C	4.0	38	—[d]
3	[(1c)$_2$Ni][OTf]$_2$	Et$_2$O, 25 °C	4.0	38	≥ 95 %
4	[(1c)NiCl$_2$]	THF, 25 °C	0.8	0	69 %
5	[(1c)NiCl$_2$]	C$_6$H$_6$ 25 °C	0.07	5	—[d]
6	[(1c)NiCl$_2$]	Et$_2$O, -19 °C	4.0	45	≥ 95 %
7	[(1c)NiCl$_2$]	Et$_2$O, -78 °C	0	—[d]	—[d]
8	[(1c)NiCl$_2$]	Et$_2$O, 25 °C	---[c]	27	—[d]
9	[(1c)NiCl$_2$]	Et$_2$O, 25 °C	---[f]	6	—[d]
10	[(1c)NiCl$_2$][g]	Et$_2$O, 25 °C	≥ 25	19	42 %
11	[(1c)$_2$Ni][OTf]$_2$	Et$_2$O, 25 °C	2.0	8[h]	≥ 95 % [h]

a: typical conditions [Ni] = 0.75 mM (1.5 mol%), [*Z*-**5**] = 50 mM, [(±)-**4**] = 125 mM. The enantiomeric excess (ee) of the cross coupling product *Z*-1,3-diphenylbutene *Z*-**6** was measured by chiral HPLC (Chiralcel OD). b: Isolated yield of pure material after column chromatography on silica-gel. c: with added 1 equivalent (1.5 mol %) **1c**, [Ni] / [**1a**] = 0.5. d: Not determined. e: Slow addition of *Z*-**5** by syringe pump over 3 h. period. f: Slow addition of (±)-**4** by syringe pump over 1.5 h. period. g: [Ni] = 0.025 mM (0.05 mol%). h: *E*-**5** was used, the ee of the product, *E*-1,3-diphenylbutene *E*-**6**, was measured by chiral HPLC (Chiralcel OD). The absolute configuration of *E*-**6** was not determined.

Westermann *et al.* have reported extensively on the use of Ni complexes and salts to catalyse [1,4] addition of trialkyl aluminium reagents to enones.[27] With nickel complexes [(**1c**)NiCl$_2$] and [(**1c**)$_2$Ni][OTf]$_2$·H$_2$O in hand, we tested the possibility of an enantioselective variant by addition of an excess of Me$_3$Al (*n*-heptane solution) at ambient temperature to solutions of chalcone in THF containing a catalytic quantity (2 mol %) of each Ni complex - Scheme 5. The two complexes, [(**1c**)NiCl$_2$] and [(**1c**)$_2$Ni][OTf]$_2$·H$_2$O, displayed very different behaviour under these conditions. Thus, on addition of Me$_3$Al, [(**1c**)NiCl$_2$] (pink-purple in THF) was rapidly reduced (≤ 5 sec.) to afford a cherry-red solution containing a reasonably active catalyst (≥ 30 turnovers per h.) and the 1,4 addition product was obtained in good yield (94 %) after 2 h.



Scheme 5 - The [1,4] addition of Me$_3$Al to chalcone catalysed by enantiomerically pure [(**1c**)NiCl$_2$] or [(**1c**)$_2$Ni][OTf]$_2$·H$_2$O.

In stark contrast, [(**1c**)$_2$Ni][OTf]$_2$·H$_2$O was found to display a considerable induction period (30 min), possibly due to the requirement for initial dissociation of one of the bidentate ligands prior to reduction, followed by a sluggish catalytic reaction (ca. 1 turnover per h). The doubled ligand / Ni ratio of [(**1c**)$_2$Ni][OTf]$_2$·H$_2$O may well be responsible for low catalyst activity by equilibrium of catalytically active [(**1c**)Ni(S)$_2$] (S = solvent, substrate or vacant site) with catalytically inert [(**1c**)$_2$Ni] species. Although complexes [(**1c**)NiCl$_2$] and [(**1c**)$_2$Ni][OTf]$_2$·H$_2$O were found to catalyse the addition process with very high [1,4] selectivity, ≥ 99.5 % and 99% respectively, neither complex induced any detectable enantioselectivity in either the 1,4 or 1,2 addition products (HPLC). In the absence of Ni catalyst, there was ca. 1 % conversion over 24h. to afford the 1,2 addition product and no detectable 1,4 product.

DISCUSSION

The preferred geometry of transition-metal complexes of phosphinoaryl oxazoline ligands bearing an alkyl or aryl substituent at the stereogenic centre is a 6-membered envelope shaped chelate (*vide infra*) (figure 3). A rationale for this chelate conformation can be envisioned by consideration of distortion from a hypothetical flat 6-membered chelate by rotation of the connecting aryl ring above (motion **A** -> λ- chelate) or below (motion **B** -> δ-chelate) the P-M-N plane (figure 3).

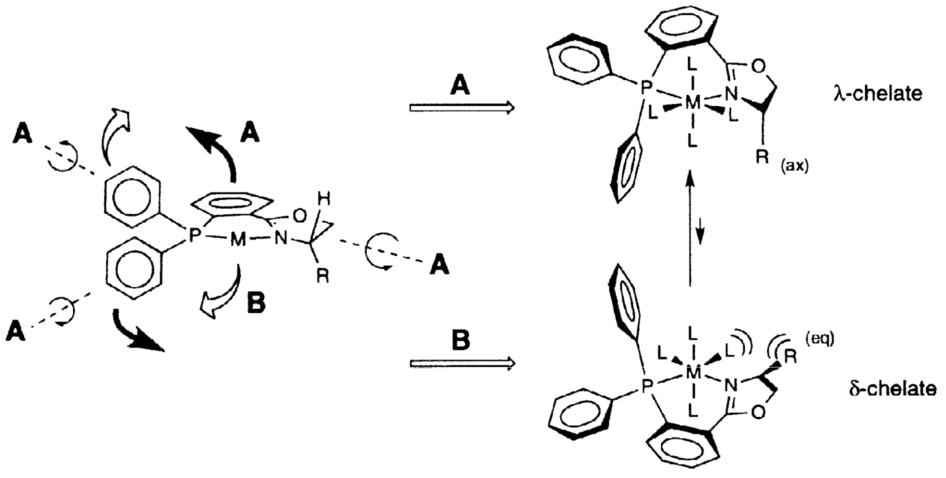


Fig 3 - Ligand distortions arising through twisting the aryl linkage above or below the P-M-N chelate plane of a hypothetical planar complex formed by coordination of P and N donors of a phosphinoaryl oxazoline ligand to a metal centre. Of note is the chiral Ph$_2$P array induced by preference for a δ or λ six-membered chelate envelope resulting from a bias for the positioning of the substituent at the oxazoline stereogenic centre in a pseudoaxial or pseudoequatorial position.

Two important effects of this rotation are the movement of the two *P*-phenyl groups up (motion **B**) or down (**A**) and the re-location of the stereogenic oxazoline substituent (R) to a pseudoaxial (motion **A**) or pseudoequatorial position (motion **B**). Since in the pseudoequatorial position the substituent (R) will encounter steric clash with the other ligands at the metal centre, the preferred geometry is expected to be that arrived at by motion **A**. Indeed, the envelope shaped P-M-N chelate ring with pseudoaxial substituent (R) has been observed in all of the published solid state structures of various transition-metal phosphinoaryl oxazoline complexes (Pd, Ir, W, Mo, Ni, Zn)[28] bearing alkyl or aryl substituents at the oxazoline stereogenic centre. The pseudoaxial *iso*-butyl substituent is clearly visible in the solid state structure of [(**1c**)$NiCl_2$] (Fig 2).

An important secondary effect of this geometric preference is to define the chelate chirality (δ or λ) and possibly also the helicity of the "edge-on" and "face-on" PPh_2 array (Fig 4). Assuming, as seems reasonable, that this geometry is also preferred in catalytic intermediates, then this chiral PPh_2 array can act as an auxiliary or even exclusive control element in the mechanism of enantioselective catalysis by complexes of this ligand type.[28b]

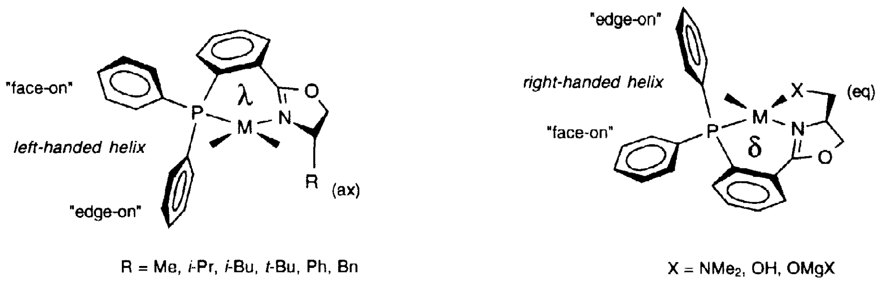


Figure 4 - Generalised (square planar) structures for metal complexes of phosphinoaryl oxazolines - showing the difference between pseudoequatorial and pseudoaxial substituent orientation on the sense of chelate chirality and spacial array of the PPh_2 group. Substituents bearing polar and coordinating functionality are expected to adopt a pseudoequatorial position if a free coordination site is available at the metal centre. This results in a switching of the chelate from λ to δ (or *vice versa* - dependent on the absolute configuration of the oxazoline stereogenic centre) and hence an inversion of the arrangement of "edge-on" and "face-on" Ph rings at the Ph_2P array.

For the ligand series **1a**-**f**, if the major pathway for the diastereoselective transmetallation reaction were to occur on the same face of the P-Ni-N ligand plane as the stereogenic center, then increasing the steric volume of the substituent could be expected to reduce rates and enantioselectivities - as is observed, Fig. 1.

In contrast to ligands **1a**-**f** with essentially inert alkyl or aryl substituents, ligands **2a** and **2b** bear polar substituents (CH_2OMgX and CH_2NMe_2 resp.) that may well interact with either the Grignard reagent or the Ni centre. Interaction with the Ni centre would necessarily require the substituent to attain a pseudoequatorial orientation and this is obtained by changing from λ to δ envelope chelate (fig 4).

If the spacial array of the Ph_2P group and not the sense of chirality at the oxazoline stereogenic centre is more important for controlling enantioselectivity, then this would invert the sense of asymmetric induction - as is observed, Table 1 (entries 8,9). Furthermore, ligand **3**, which lacks a rigid planar connection between the oxazoline and the Ph_2P group, fails to induce any enantioselectivity, this again suggesting that it is the spacial array of the Ph_2P group that is the relay for transmission of the chiral information from the oxazoline to substrate.

CONCLUSIONS

The cross-coupling of (±)-**4** with *Z*-**5** catalysed by Ni-phosphinoaryl oxazoline complexes of ligands **1**, **2** and **3** has an enantioselection maxima of ca. 41 % ee (at 25 °C). The stereogenic substituent on the oxazoline ring of the ligand provides a bias for either the λ or the δ envelope P-Ni-N chelate. This bias can be provided by steric effects (ligands **1**a-f) in which the substitutent is pseudoaxial or by polar functionality (ligands **2**a and 2b) in which the substitutent is pseudoequatorial and it is the bias that controls the sense of chirality of the Ph_2P array. The results obtained with the series of ligands **1**, **2** and **3**, suggest that the chiral array of the Ph_2P unit is the active control element for the diastereoselective step in the cross-coupling reaction of (±)-**4** with *Z*-**5**.

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EXPERIMENTAL

General All manipulations were performed on a vacuum line (argon) using standard Schlenk techniques. Before use, THF, *t*-BuOMe and Et_2O were freshly distilled from Na / benzophenone, de-gassed (freeze-thaw cycles) and argon saturated. NMR: Varian Gemini 300 or VXR400 and JEOL GX400, ^1H and ^{13}C data reported as ppm from TMS, ^{31}P data reported as ppm and referenced to $(PhO)_3P=O$ (-18 ppm). IR: Perkin-Elmer 1600 FT, data reported in cm^{-1}. MS: Varian MAT 212, FAB matrix: 3-nitrobenzyl alcohol data reported as m/z isotope cluster calc.(obs.). HPLC: *Daicel Chiralcel OD* column (25 x 0.46 cm) with pre-column (5.0 cm), detecting at 254 nm. Flash chromatography: Chemie Uetikon C560 silica gel (35 - 70 μm).

1-Phenethyl magnesium chloride (±)-**4** Magnesium turnings (23g, 0.95 mol) were activated[19] under argon by dry-stirring vigorously, in a large Schlenk tube with a magnetic follower, for up to 14 days. After addition of sufficient Et_2O to cover the activated Mg (ca. 40 ml), the slurry was cooled to 0 °C and vigorously stirred during dropwise addition of 1-phenyl ethyl chloride[29] (5.48 g, 0.04 mol) in Et_2O (100 ml) over 12h. After warming to 25 °C, the grey-black reaction mixture was filtered *via* cannula through two sintered-glass frits (grades 2 then 4) to afford a clear pale-yellow Et_2O solution of (±)-**4** that titrated as 0.29 M and was stored at RT.

E-β-Bromostyrene (*E*)-**5**. A sample of ca. 85% *E*-, 15 % *Z*-β-bromostyrene (Fluka) (10 g, 55 mmol) of was dissolved in *i*-PrOH, 100 ml. NaOH (1.6 g, 40 mmol) was added and then the mixture refluxed under argon for 2h., cooled to 20 °C (1h.) and carefully diluted with water (100 ml). The mixture was extracted with two 100 ml portions of pentane and the combined extracts dried ($MgSO_4$) then evaporated to afford a brown oil that was purified by distillation (57-59 °C, 2 mmHg) to afford >99.9 %*E*-β-bromostyrene.

Z-β-Bromostyrene (*Z*)-**5**. Cinnamic acid (16 g, 0.108 mol) in $CHCl_3$ (250 ml) at 0 °C was treated dropwise over a period of 1h. with a solution of Br_2 (6 ml, 18.6 g, 0.116 mmol) in $CHCl_3$ (60 ml). After purification, the dibromide (11.5 g) was mixed with anhydrous Na_2CO_3 (8.3g) and acetone (200 ml). The mixture was refluxed for 18 h with protection from light, cooled to 25 °C, evaporated and the resultant white paste extracted with pentane (5 x 50 ml). The combined extracts were dried (Na_2SO_4), evaporated and distilled (39-39.5 °C, 1.5 mmHg) to afford ≥ 99.9 % *Z*-β-bromostyrene.

Preparation of [(**1**c)$NiCl_2$] $NiCl_2$ (152 mg, 1.17 mmol) and ligand **1**c (475 mg, 1.23 mmol) were mixed thoroughly and dried by stirring vigorously *in vacuo*. Under argon, THF (20 ml) was added resulting in rapid dissolution of **1**c and a surface reaction on the $NiCl_2$ (yellow to red). The mixture was vigorously stirred and then heated to 60 °C for 25 minutes resulting in a red-purple solution. After cooling to 25 °C, the solution was filtered through a 25 micron HPLC filter to remove traces of unreacted $NiCl_2$ then concentrated *in vacuo* to 5 ml and carefully layered with *t*-BuOMe (30 ml). After complete diffusion (24 h.) the resultant deep purple blocks were separated, washed with *t*-BuOMe (6 x 5 ml) and dried *in vacuo* to afford [(**1c**)NiCl$_2$] (313.4 mg, 52%). m.p. 190-194 °C (from THF / *t*-BuOMe). Found: C, 58.1; H, 5.0; N, 2.7. $C_{25}H_{26}Cl_2NOPNi$ requires C, 58.1; H, 5.1; N, 2.7. IR(KBr) 3424*m*, 3050*m*, 3013*w*, 2958*s*, 2868*s*, 1626*s*, 1592*m*, 1566*m*, 1482*s*, 1468*m*, 1436*s*, 1374*s*, 1318*m*, 1275*m*, 1250*m*, 1235*m*, 1202*w*, 1147*s*, 1125*m*, 1101*s*, 1059*m*, 1027*m*, 997*m*, 964*m*, 948*m*, 930*m*, 893*w*, 851*w*, 831*w*, 783*m*, 750*s*, 714*m*, 692*s*. ^{1}H NMR (CDCl$_3$) -7.4 (s, 1H); -4.3 (s, 1H); -3.8 (s, 1H); -1.2 (bs, 2H); 0.7 (bs, 2H); 1.3 (s, 1H); 1.4 (s, 1H); 3.2 (s, 4H); 3.3 (s, 1H); 3.8 (s, 3H); 6.7 (bs, 1H); 9.3 (s, 1H); 9.6 (bs, 1H); 11.0 (s, 1H); 20.0 (s, 2H); 21.2 (s, 2H); 22.1 (s, 1H). ^{13}C NMR (CDCl$_3$) 16.4, 26.0, 31.2, 51.3, 117.4, 132.6, 142.1, 200.7, 203.4, 222.8, 249.0, 393.5, 410 (b) 444 (b), 456 (b). ^{31}P NMR (CDCl$_3$) 31.3 (bs). MS(FAB) [(**1c**)$_2$Ni$_2$Cl$_3$]$^+$ 1003(limit) - 995 calc.(obs.) 6(5) 3(3) 11(11) 6(5) 10(10) 5(4) 5(4) 2(2) 2(1); [(**1c**)$_2$NiCl]$^+$ 867 - 871 calc.(obs.) 4(4) 2(1) 3(3) 2(1) 1(1); [(**1c**)$_2$Ni]$^+$ 832 - 837 calc.(obs.) 39(39) 23(22) 22(22) 11(10) 5(5) 2(1); [(**1c**)NiCl]+ 480 -487 calc.(obs.) 100 (100) 28(27) 74(73) 22(20) 21(20) 6(6) 4(4)1(1); [(**1c**)Ni]$^+$ 445 - 452 calc.(obs.) 54 (54) 15(19) 23(20) 7(7) 4(4) 1(1).

Preparation of [(**1c**)$_2$Ni][OTf]$_2$·H$_2$O To ligand **1a** (35 mg, 0.09 mmol), [(**1c**)NiCl$_2$] (42.5 mg, 0.082 mmol), and AgOTf (42.2 mg, 0.164 mmol) was added degassed THF (2.5 ml) resulting in the rapid generation of an orange solution and white suspension. After stirring for 5 min., the mixture was filtered through a small pad of Celite. The Celite pad was washed with THF (2.5 ml) and the combined filtrates evaporated to afford a viscous orange oil. The oil was dissolved in CH$_2$Cl$_2$, filtered through Celite, washing through with 2 x 1 ml CH$_2$Cl$_2$ to afford a clear orange filtrate. Addition of *t*-BuOMe (8 ml) followed by slow concentration by rotary evaporation (48 °C, 770 mmHg, selectivly removing CH$_2$Cl$_2$) afforded a crystalline deposit that was separated, washed with *t*-BuOMe (3 x 5 ml) and dried *in vacuo* to afford [(**1c**)$_2$Ni][OTf]$_2$·H$_2$O as an orange crystalline solid (90.9 mg, 97 %). m.p. (darkens at ca. 100°C) melts at 225-226°C. Found: C, 54.2; H, 4.7; N, 2.4. $C_{52}H_{52}N_2O_8S_2F_6P_2Ni$ requires C, 54.3; H, 4.7; N, 2.4. IR (KBr) 3130*w*, 3066*m*, 3007*w*, 2960*s*, 2887*m*, 1628*s*, 1592*w*, 1581*m*, 1570*m*, 1557*w*, 1487*m*, 1438*s*, 1395*s*, 1371*w*, 1351*w*, 1263*s*, 1231*w*, 1224*s*, 1198*w*, 1153*s*, 1112*m*, 1098*s*, 1063*w*, 1031*s*, 999*w*, 945*w*, 926*m*, 786*w*, 744*m*, 714*m*, 693*m*, 637*s*. ^{1}H NMR (CDCl$_3$) 0.82 (*d*, *J* = 6.3, 3H, CH(C$\underline{H}_3$)$_2$) 0.83 (*d*, *J* = 6.0, 3H, CH(C$\underline{H}_3$)$_2$); 1.43 (*m*, 1H, C$\underline{H}_2$CH(CH$_3$)$_2$; 2.05 (*m*, 1H, C$\underline{H}$(CH$_3$)$_2$; 2.37 (*m*, 1H, C$\underline{H}_2$CH(CH$_3$)$_2$; 4.07 (*dd*, *J* = 9.0, 8.1, 1H, C$\underline{H}_2$O); 4.40 (*m*, 1H, C$\underline{H}$N); 5.45 (*dd*, *J* = 9.3, 9.0, 1H, C$\underline{H}_2$O); 7.33 (*m*, 2H, CH arom.); 7.48 (*m*, 4H, CH arom.); 7.62 (*m*, 3H, CH arom.); 7.72 (m, 2H, CH arom.); 7.84 (*m*, CH arom.); 8.11 (*d*, *J* = 8.7, 1H, CH arom.). ^{31}P NMR (CDCl$_3$) 24.5 (s). MS (FAB) [(**1c**)$_2$Ni(O$_3$SCF$_3$)]$^+$ 981 - 985 calc.(obs.) 13(13) 8(7) 8(8) 4(4) 2(1); [(**1c**)$_2$Ni]$^+$ 832- 837 calc.(obs.) 56(56) 32(31) 31(30) 15(14) 7(8) 3(2); [(**1c**)Ni(O$_3$SCF$_3$)]$^+$ 594 - 600 calc.(obs.) 100(100) 31(29) 48(47) 15(16) 10(9) 3(3) 2(2); [(**1c**)Ni]$^+$ 445 - 451 calc.(obs.) 68(68) 20(23) 29(26) 9(8) 5(4) 1(1) 1(1).

Ni-catalysed Grignard Cross-coupling The following procedure for the preparation of *Z*-3*S*-1,3-diphenyl butene *Z*-**6** is typical. In an ampoule equipped with a Young valve and magnetic stirring bar, a suspension of [(**1c**)NiCl$_2$] (2.2 mg, 4.25 μmol, 1.5 mol%) in a degassed, argon saturated solution of *Z*-**5** (50 mg, 0.273 mmol) in Et$_2$O (1.5 ml) was frozen (liq. nitrogen) and treated under argon with a solution of (±)-**4** in Et$_2$O (4 ml of 0.17M, 0.68 mmol). The ampoule was sealed and then immersed in a thermostatted cooling bath (-19 °C). The mixture rapidly became an homogenous orange-brown solution followed by precipitation of magnesium salts (1-2 minutes). TLC analysis (pentane) indicated complete conversion (R$_f$ *Z*-**5** 0.62; *Z*-**6** 0.38) and the reaction was quenched by addition of an aqueous solution of NH$_4$Cl (6 ml, 2.8 M). After warming to ambient temperature, the mixture was extracted with CH$_2$Cl$_2$ (5 x 10 ml), the combined extracts dried (Na$_2$SO$_4$) and evaporated to afford a pale yellow oil that was purified by flash chromatography on silica-gel (2 x 25 cm) eluting with pentane and collecting 42 x 15 ml fractions. Fractions 26-38 (R$_f$ 0.38) were combined and evaporated to afford *Z*-3*S*-1,3-diphenyl butene **6** as a pale yellow oil (60.4 mg, quantitative). HPLC analysis 45 % ee (0.1 % iPrOH, 99.9 % hexane, 0.5 ml min^{-1}, T$_R$ (*R*) 16.70; (*S*) 21.50 min)

Ni-catalysed 1,4 addition of Me$_3$Al to chalcone Chalcone (100 mg, 0.48 mmol) and [(**1c**)NiCl$_2$] (5.7 mg, 0.01 mmol) were dissolved in THF (5 ml) and the resultant pale pink solution degassed then argon saturated. At 25 °C, a solution of Me$_3$Al (2.0 M in heptane, 0.3 ml, 0.6 mmol) was added in one portion resulting in a rapid deepening of the solution to a cherry-red colour. After 100 min., TLC analysis indicated that all of the chalcone had been consumed and the reaction was carefully quenched by addition of NH$_4$Cl (5 ml, 2.8 M). After gas evolution had subsided, the red (two-phase) mixture was stirred for 5 min. resulting in a single-phase red solution that was carefully extracted with CH$_2$Cl$_2$ (3 x 20 ml). The colourless extracts were dried (Na$_2$SO$_4$) and evaporated to afford a pale yellow oil that was purified by flash chromatography on silica-gel (2 x 25 cm) eluting with 19:1 *n*-hexane/EtOAc and collecting 16 x 20 ml fractions. Fractions 11-15 (R$_f$ 0.34) were combined and evaporated to afford 4-phenyl pentan-2-one as a white solid (99.1 mg, 93.3%). HPLC analysis 0 % ee (0.3 % iPrOH, 99.7 % hexane, 0.5 ml min^{-1}, T$_R$ 58.2 and 66.1 min).

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