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Asymmetric Grignard Cross-Coupling Reaction: An Investigation of the Factors Influencing Asymmetric Induction with a New Type of Pyrrolidinephosphane

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An investigation of the asymmetric synthesis of 3-phenyl-1-butene by the Grignard cross-coupling reaction is presented. The reaction is catalysed by nickel complexes of bisphosphane and 3-diphenylphosphanylpyrrolidine-type ligands. A comparison of the results obtained with our P,N monophosphane ligands with those obtained with the most effective known amino acid derived P,N ligands shows a similar enantioselectivity but an inverse sense of optical induction. An X-ray structural analysis of the 1-phenylethyl Grignard compound is reported. Quantitative analysis and the determination of enantiomeric composition of the catalytic samples is accomplished using a novel enantioselective GLC separation. Compared to the popular model reaction that uses a chloride-containing Grignard compound and vinyl bromide as starting compounds, we obtain improved enantioselectivities of P,N monophosphane catalysts by substituting vinyl bromide with vinyl chloride. With two of the new P,N ligands we find a nonlinear dependence of enantioselectivity on the enantiomeric purity of the ligands (asymmetric amplification). Catalytic results subject to such nonlinear effects show a dependence on the ligand to nickel ratio.

Introduction

Carbon–carbon bond formation by cross-coupling of main group organometallics with carbon electrophiles catalysed by transition metal complexes is a valuable tool in organic chemistry[1]. Among the transition metal compounds used for the efficient synthesis of substituted aryl-, vinyl-, and allylic compounds, copper reagents and nickel- and palladium phosphane complexes have proved to be most effective. When chiral phosphanes are used as ligands for nickel or palladium, chiral organic products can be prepared enantioselectively from racemic or prochiral reagents. This type of reaction has recently been reviewed by Hayashi[2]. The coupling of a racemic secondary organomagnesium or organozinc reagent with an achiral aryl- or vinyl halide is called the Grignard cross-coupling reaction. Research in this field of catalysis has focused on two important reactions.

The first reaction is the coupling of the Grignard compounds prepared from racemic 2-halobutanes with halobenzenes. The main finding of work carried out by Consiglio[3] was that the enantioselectivity of this reaction can be influenced by variation of the solvent, the halogens used, and the molar ratio of the two organic starting compounds. Consiglio used nickel complexes with chelating phosphanes based on a 1,2-bis(diphenylphosphanyl)ethane skeleton. Such ligands reduce the amount of cross-coupling products that are formed by isomerisation of the 2-butyl group[4]. A catalyst prepared in situ from $NiCl_2$ and two galactose-derived monophosphane ligands has been shown to yield the desired 2-phenylbutane in even higher chemical and optical yields[5].

The coupling of vinyl halides **1a** or **1b** with the Grignard compounds **2a** or **2b** prepared from racemic 1-halo-1-phenylethane yields 3-phenyl-1-butene (**3**) (Scheme 1)[2]. This compound has synthetic utility as a starting material for the synthesis of commercial chiral products, e.g. non-steroidal antiflammatory drugs[6]. Consiglio and Indolese compared catalytic results obtained with a nickel complex of (1*R*,2*R*)-1,2-bis(diphenylphosphanyl)cyclopentane (**DPCP**) with those obtained using a nickel complex of a ferrocenyl bisphosphane with an additional (dimethylamino)alkyl ligating site[7]. By monitoring the change of enantiomeric excess (% ee) as a function of extent of conversion by enantioselective GLC, they showed that enantioselectivity in catalytic runs with a nickel complex of **DPCP** is strongly dependent on the extent of conversion. The nickel complex of the second ligand with an additional (dimethylamino)alkyl ligating site was shown to be the more enantioselective catalyst and the enantioselectivity did not change during the course of

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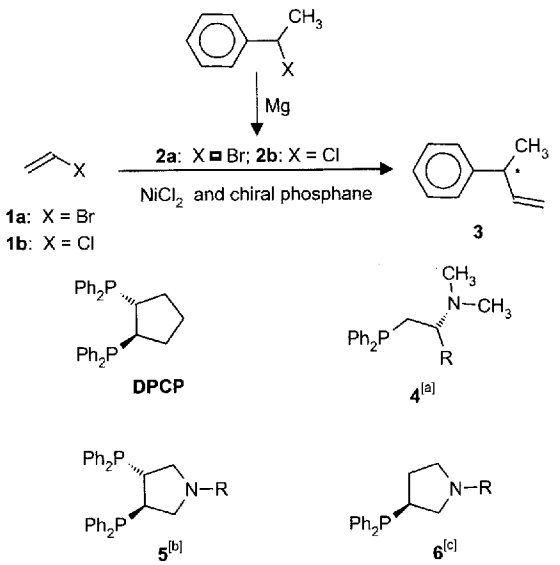
the reaction. Changes in enantioselectivity with extent of conversion are related to changes in the nature of the transmetallating Grignard compound[7].

Complexes of P,N (type **4**) monophosphanes with (dimethylamino)alkyl ligating sites are the most enantioselective catalysts in this nickel-catalysed reaction[8]. Here, we describe an investigation of this catalysis in which either isolated $NiCl_2$ complexes of bisphosphane ligands (**5a** and **5b**) or in situ prepared nickel complexes of novel P,N monophosphanes have been employed. The preparation of **6** and **6a–c** has been reported recently[9]. We also report herein a novel, quantitative analytical method based on enantioselective GLC.

Scheme 1. Catalytic asymmetric cross-coupling of Grignard compounds **2a** or **2b** with vinyl halides **1a** or **1b** yielding chiral 3-phenyl-1-butene (**3**); chiral phosphanes relevant to this paper are shown below



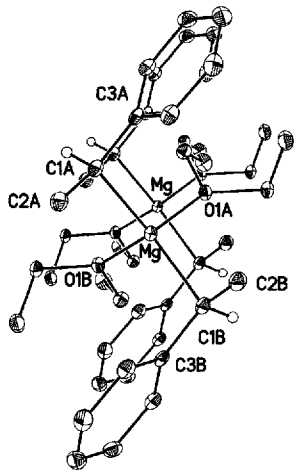
[a] (*S*)-**4a** (R = *i*Bu), (*S*)-**4b** (R = *s*Bu), (*S*)-**4c** (R = *t*Bu), (*S*)-**4d** (R = Bzl). – [b] **5a** (R = Bzl), **5b** (R = Boc). – [c] (*S*)-**6** (R = H), (*S*)-**6a** (R = Bzl), (*S*)-**6b** (R = 2-methoxybenzyl), (*S*)-**6c** (R = Et).

Results and Discussion

Preparation and X-ray Structure of Grignard Compound 2b

Since Brown and coworkers published an improved preparation of **2b** and related benzylic Grignard compounds in 1991[10] the problems due to dimerisation of benzylic radical anions (homo-coupling) during the synthesis have been overcome. In our preparations however, one difference between the description of Brown and our experimental observations was quite obvious. Working at −10 °C to 0 °C, we observed extensive formation of $MgCl_2$, which could be separated by filtration through Celite. On removal of an aliquot from the clear filtrate and hydrolysis of the Grignard compound **2b**, quantitative analysis of the phenylethane content of the resulting ethereal solution by GLC (vide infra) revealed that **2b** contained at least 0.35 mol/l (88% yield) of benzylic anions. The amount of $MgCl_2$ filtered off could not be attributed to the homo-coupling reaction alone. From stock sulutions stored at 4 °C in a refrigerator, additional $MgCl_2$ and a few small, pale-yellow crystals invariably separated. On one occasion, these crystals were large enough to allow an X-ray structure investigation. The results are presented in Figure 1.

Figure 1. X-ray structure of **2b**; the vector connecting both Mg atoms is a crystallographic C_2 axis pointing in the same direction as the *b* axis; the Mg–Mg distance equals the *b* axis length[a]



[a] Selected bond lengths [Å] and angles [°]: Mg–O(1A) = Mg–O(1B) 2.0575(10), Mg–C(1A) = Mg–C(1B) 2.1953(13), C(1A)–C(3A) = C(1B)–C(3B) 1.473(2), C(1A)–C(2A) = C(1B)–C(2B) 1.532(2); O(1A)–Mg–O(1B) 93.83(6), C(1A)–Mg–C(1B) 122.18(7), C(3A)–C(1A)–C(2A) 115.10(11), C(2A)–C(1A)–Mg 109.30(9), C(3A)–C(1A)–Mg 107.99(8).

A halide-free bis(1-phenylethyl)magnesium compound coordinated by two additional diethyl ether molecules is shown. The observation of $MgCl_2$ precipitation from solutions of Grignard compound **2b** can thus be explained; disproportionation leads to $MgCl_2$, which is only sparingly soluble in diethyl ether, and to the bis(1-phenylethyl)magnesium compound, which remains in solution. This result has great relevance for the understanding of the cross-coupling reaction with Grignard compound **2b**. In our experimental procedure, the Grignard solution is cooled to below −40 °C prior to the addition of the vinyl halide, and on doing so we always observed extensive precipitation of $MgCl_2$. The bis(1-phenylethyl)magnesium compound might therefore be the actual species involved in transmetallation to the nickel complex. In all recent mechanistic discussions such a possibility has never been taken into consideration. The nature of the magnesium species which transfer their alkyl groups to the transition metal catalyst can change during course of the reaction, because reactions of Grignard compounds in solution[11] are affected by, for example, dilution and the concentration of dissolved magnesium halides.

It has been shown that racemisation rates[10,12] of secondary benzylic Grignard compounds such as **2b** are slow compared to the rate of the cross-coupling reaction. It cannot be ruled out that the observed changes in enantioselectivity with extent of conversion in catalytic runs with bisphosphane complexes are due to a kinetic resolution[13] of the Grignard compound **2b**. A catalyst able to induce epimerisation of an alkyl group bound to the transition metal should not, however, be influenced by the enantiomeric

composition of the Grignard compound **2b**. It is known that nickel complexes which are able to induce isomerisation of coordinated alkyl groups by a series of σ-π interconversions can also induce epimerisation of these alkyl groups[4].

In Figure 1, the stacking of two bis(1-phenylethyl)magnesium molecules along the crystallographic C_2 axis (space group *C*2/c) is shown. The first 1-phenylethyl group bound to Mg is transformed to the second (C_2 axis) indicating an *R,R* or *S,S* configuration of the asymmetric carbon centres. Each such stack of enantiomerically pure molecules (e.g. *R,R*) is accompanied by a second with *S,S* configuration, generated by a crystallographic inversion. Overall, the crystal is therefore of racemic composition. The bond lengths and angles given in Figure 1 are all in accord with published data of analogous dialkylmagnesium compounds[14].

Experimental Set-Up Used for Catalytic Runs

All catalytic runs were performed by adding the Grignard compound **2b** at −78 °C to a suspension of the nickel(II) phosphane complex containing 50 μmol of Ni. Catalytic runs with bisphosphane ligands **5a**, **5b** were carried out with isolated $NiCl_2$ complexes[15,16] as catalyst precursors. Catalytic runs with the P,N monophosphane ligands **6**, **6a**−**c** were carried out with nickel complexes prepared in situ. The $NiCl_2$ used was prepared from $Ni(OAc)_2 \cdot 4\ H_2O$ and acetyl chloride[17]. The brown powder was dried in vacuo at 180 °C for 18 hours and then several weighed amounts were dissolved in water. The nickel content was assayed by complexometric titrations with EDTA against murexide[18]. Based on this analysis, a sample of $NiCl_2$ containing 50 μmol of Ni was reacted with a diethyl ether solution containing 55 μmol of phosphane so as to obtain a catalyst of L/Ni = 1 composition.

Reactions were terminated by hydrolysis. For quantitative analysis of the hydrolysed reaction mixtures by means of enantioselective GLC, a known amount of mesitylene was added as an internal standard[19]. The quantitative analysis of the samples containing the rather volatile products 3-phenyl-1-butene (**3**), phenylethane, and styrene was quite laborious and difficult until a report of Brunner, König, and coworkers demonstrated that by GLC on a 40 m LIPODEX C (perpentylated β-cyclodextrin) column, both the quantitative analysis and the enantiomeric composition could be determined simultaneously[16]. The main drawbacks of this method are the long analysis times (t = 80 min) and the analysis temperature of 28 °C, which is outside the range of reliable temperature control with commercial GC instruments[19]. In 1991, Keim et al., published an enantiomer separation of **3** using a permethylated β-cyclodextrin/polysiloxane phase[20]. We used a 60-m phase-II column, purchased from CS-Chromatography Service[21], which allowed a reduction of the analysis time to 30 min and separations to be conducted at 70 °C and 0.85 bar H_2. The retention data (selectivity factors α[19]) of the compounds of interest are collected in Table 4. The elution order of enantiomers {(*R*)-**3** before (*S*)-**3**} and of other compounds is similar to the separation on LIPODEX C.

Table 1. Collection of GLC parameters[a]

Compound	Selectivity factor α [b]	Response factor $f_{(mol)}$ [c]
Phenylethane	2.28	1.137
Styrene	2.78	1.125
Mesitylene	3.49	1
(*R*)-**3**	5.34	0.922
(*S*)-**3**	5.45	0.922
4-Phenyl-1-butene	6.94	0.922

[a] The separation conditions are discussed in the text. − [b] α = 1 for diethyl ether with retention time t_R = 3.8 ± 0.3 min. − [c] The relative molar response factor is given; $f_{(mol)}$ = 1 for mesitylene (internal standard).

We used a gas chromatograph with split injection and FID detector. The conversion of the recorded FID peak areas of eluted compounds into quantities (in mmol) of the corresponding sample components could be effected via "relative molar response factors" $f_{(mol)}$[19]. These $f_{(mol)}$ factors were determined from a series of calibration measurements using standard solutions containing mesitylene, phenylethane, styrene and 4-phenyl-1-butene at concentrations in the ranges expected in our samples. 4-Phenyl-1-butene (Aldrich) was used as a substitute of a pure standard of isomeric compound **3**. The response factors $f_{(mol)}$ of the compounds, with $f_{(mol)}$ = 1 for mesitylene, are collected in Table 4.

Varying amounts of each sample were injected and analysed in order to evaluate the reproducibility[19] of our analytical method. A comparison of the results showed that the determinations of the quantities of sample components were reproducible to within less than ±0.05 mmol, and that enantiomeric excess (% ee) values were reproducible to within less than ±0.5% in the GLC analysis.

Table 2. Catalytic results with isolated $NiCl_2$ complexes of **5a** and **5b** (50 μmol Ni) in diethyl ether

Entry	Ligand	Vinyl halide	Yield (% [a])	**3** % ee (confign.)	ln (*R*/*S*)	Number of catalytic runs
1	**5a**	**1a** [b]	50 - 94	17 (*S*)	-0.33	3 [f]
2	**5a**	**1b** [b]	70	6 (*S*)	-0.12	1
3	**5b**	**1a** [b]	64 - 98	28 (*S*)	-0.58	3 [g]
4	**5b**	**1b** [b]	64 - 78	23 (*S*)	-0.46	3 [e]
5	**5a**	**1a** [c]	90	5 (*S*)	-0.10	1
6	**5a**	**1b** [c]	52, 70	3 (*S*)	-0.06	2 [d]
7	**5b**	**1a** [c]	78	23 (*S*)	-0.46	1
8	**5b**	**1b** [c]	46[h]	31 (*S*)	-0.64	1

[a] The yield is based on the amount of vinyl halide used. − [b] 6 mmol **2b** and 5 mmol of vinyl halide used. − [c] 12 mmol **2b** and 5 mmol of vinyl halide used. − [d] σ[ln(*R*/*S*)] = 0.04. − [e] σ[ln(*R*/*S*)] = 0.05. − [f] σ[ln(*R*/*S*)] = 0.07. − [g] σ[ln(*R*/*S*)] = 0.09. − [h] 75% of **2b** used was recovered as phenylethane in the hydrolysed reaction mixture.

Catalysis with $NiCl_2$ Complexes of Bisphosphane Ligands 5a, 5b

We investigated the influence of the halogen in vinyl halides **1a** and **1b**, and of the Grignard compound **2b** to vinyl

halide ratio on enantioselectivity in the cross-coupling reaction with isolated nickel complexes of **5a** and **5b** (Table 2). In catalytic runs with different **2b** to vinyl halide ratios, the starting concentration of **2b** was maintained. We will use ln(*R*/*S*) values[22], which can be easily calculated from % ee values, as an enantioselectivity scale in our discussion. The absolute standard deviations σ of repeated catalytic runs (Table 2) indicate that the reproducibility of a ln(*R*/*S*) value in GLC analysis is several times better compared to the reproducibility of a catalytic run.

The small ln(*R*/*S*) values found are in the expected[7,16] range for catalysis with bisphosphane complexes. **5a** and **5b** are interesting ligands because they are derivatives of **DPCP** bearing an additional β-amino group which might also participate in the catalytic cycle[23]. However, comparison of the ln(*R*/*S*) values for **DPCP** [ln(*R*/*S*) = −0.22] with entries 1 and 3 in Table 2 shows that the increase of enantioselectivity is too small to establish such a contribution.

The differences Δ in ln(*R*/*S*) values between catalytic runs with the same nickel complex but with different vinyl halides [compare e.g. entries 1 with 2 (Δ = 3σ) or 3 with 4 (Δ = 1.3σ)] or with different **2b** to vinyl halide ratios [compare e.g. entries 1 with 5 (Δ = 3σ) or 4 with 8 (Δ = 3.5σ)] are significant. These observations are consistent with results presented by Consiglio and Indolese, which showed that enantioselectivity in catalytic runs with nickel complexes of bisphosphanes is strongly dependent on the nature of transmetallating species[7].

Chemical yields of 3-phenyl-1-butene (**3**) in catalytic runs starting with 5 mmol of vinyl halide and 6 mmol or 12 mmol of Grignard compound **2b** vary considerably (cf. Table 2). The amounts of phenylethane found in the hydrolysed reaction mixtures indicate that approximately 5.5 mmol of Grignard compound **2b** is consumed by 5 mmol of vinyl halide. The formation of styrene and homo-coupling of the Grignard compound are known side reactions. Less than 0.2 mmol of styrene could be detected.

Table 3. Enantioselectivity of nickel P,N monophosphane (**6**, **6a**–**c**) catalysts in diethyl ether; conditions: 5 mmol of vinyl chloride (**1b**) and 6 mmol of Grignard compound **2b**; 50 μmol of Ni; ligand-to-nickel ratio 1

Entry	Ligand (% ee)	Yield (% [b])	**3** % ee (confign.)	ln (*R*/*S*)	Number of catalytic runs
1	(*R*)-**6** (98±2)	52	9 (*S*)	-0.17	1
2	(*R*)-**6a** (98±2)	64, 68	88.5 (*S*)	-2.80	2
3	(*S*)-**6b** (94±2)	48 - 64	75.0 (*R*)	1.95	3
4	(*S*)-**6c** (94±2)	50, 82	71.5 (*R*)	1.79	2
5 [a]	(*S*)-**6a** (91±2)	58, 62	88.0 (*R*)	2.75	2
6 [a]	(*R*)-**6a** (72±2)	72, 82; 52	79.5 (*S*)	-2.17	3 [d]
7 [a]	(*R*)-**6b** (72±2)	60, 72; 44	70.5 (*S*)	-1.75	3 [c]

[a] Ligands with lower enantiomeric purities. – [b] The yield is based on the amount of **1b** used. – [c] 4 mmol of **2b** used. – [d] 3 mmol of **2b** used.

Catalysis with $NiCl_2$ Complexes of P,N Monophosphane Ligands

Catalytic results obtained with nickel complexes of the secondary amine ligand **6** and *N*-alkylated derivatives **6a**–**c** are collected in Tables 3–5. We have included catalytic results that were obtained with nickel complexes with ligands of different enantiomeric purities in the Tables (vide infra). The ln(*R*/*S*) values obtained in repeated catalytic runs with *N*-alkylated derivatives **6a**–**c** with a constant set of parameters are reproducible, with absolute standard deviations σ < 0.05. Exceptions found for catalytic runs with nickel complexes of (*S*)-**6c** (94% ee) are indicated in the Tables. It is important to note that reproducibility of % ee values in GLC analysis parallels the reproducibility of catalytic runs in the case of high optical yields (cf. entries 2 in Table 3 and Table 4).

Table 4. Enantioselectivity of nickel P,N monophosphane (**6**, **6a**–**c**) catalysts in diethyl ether; ligand-to-nickel ratio 2 or 3 (entry 8) instead of 1 in Table 3; conditions: same as in Table 3

Entry	Ligand (% ee)	Yield (% [b])	**3** % ee (confign.)	ln (*R*/*S*)	Number of catalytic runs
1	(*R*)-**6** (98±2)	46	6 (*S*)	-0.12	1
2	(*R*)-**6a** (98±2)	44	88.0 (*S*)	-2.75	1
3	(*S*)-**6b** (94±2)	67; 44	73.5 (*R*)	1.88	3 [c]
4	(*S*)-**6c** (94±2)	79, 46	62.0 (*R*)	1.45	2 [d]
5 [a]	(*S*)-**6a** (91±2)	72	85.5 (*R*)	2.55	1
6 [a]	(*R*)-**6a** (72±2)	66	75.0 (*S*)	-1.95	1
7 [a]	(*R*)-**6b** (72±2)	74	67.5 (*S*)	-1.64	1
8	(*S*)-**6c** (94±2)	53	57.5 (*R*)	1.31	1

[a] Ligands with lower enantiomeric purities. – [b] The yield is based on the amount of **1b** used. – [c] 4 mmol of **2b** used. – [d] σ[ln(*R*/*S*)] = 0.07.

Chemical yields of 3-phenyl-1-butene (**3**) are collected in Tables 3–5. The highest yields (80–100%) are obtained in catalytic runs employing 5 mmol of vinyl bromide (**1a**) and 6 mmol of Grignard compound **2b** (cf. Table 5). The amounts of phenylethane found in the hydrolysed reaction mixtures indicate that approximately 5.5 mmol of Grignard compound **2b** is consumed by 5 mmol of vinyl bromide (**1a**). The use of vinyl chloride (**1b**) instead of vinyl bromide (**1a**) (cf. Table 3) results in smaller yields of **3** (70–90%). We find that only 4–5 mmol of Grignard compound **2b** is consumed under this set of reaction conditions. Yields of 3-phenyl-1-butene (**3**) are further decreased when a ligand to nickel ratio of 2 is used in catalytic runs with vinyl chloride (**1b**) and Grignard compound **2b** (cf. Table 4). Under such conditions, only 3–5 mmol of Grignard compound **2b** is consumed. Catalytic runs starting with a smaller amount (3–5 mmol) of Grignard compound **2b** and 5 mmol of vinyl halide give lower yields of 3-phenyl-1-butene (**3**). The amounts of phenylethane found in the hydrolysed reaction mixtures indicate that the reaction is terminated under all sets of reaction conditions when 90% of the Grignard compound **2b** is consumed. Because there is no clear-cut trend to indicate that a small variation of the **2b** to vinyl halide ratio has any influence on the enantioselectivity of the P,N

monophosphane catalysts, we have combined such catalytic runs as a single entry in Tables 3–5. This finding is consistent with the results presented by Consiglio and Indolese, that when nickel complexes with ligands bearing an additional tertiary amine ligating site (P,N ligands) are used, enantioselectivity does not change during the course of the reaction[7].

Table 5. Effect of ligand structure on the enantioselectivity of nickel P,N monophosphane (**6**, **6a–c**) catalysts in diethyl ether[a,b]

Entry	Ligand (% ee)	Yield (% [c])	**3** % ee (confign.)	ln (*R*/*S*)	Number of catalytic runs
1	(*R*)-**6** (98±2)	42	10 (*S*)	-0.19	1
2	(*R*)-**6a** (98±2)	98	74.5 (*S*)	-1.92	1
3	(*S*)-**6b** (94±2)	99; 56	67.0 (*R*)	1.62	2 [g]
4	(*S*)-**6c** (94±2)	82, 99	68.0 (*R*)	1.66	2 [e]
5 [b]	(*S*)-**6a** (91±2)	96	73.0 (*R*)	1.86	1
6 [b]	(*S*)-**6a** (91±2)	72	54.0 (*R*)	1.21	1 [d]
7 [b]	(*R*)-**6a** (72±2)	92	72.0 (*S*)	-1.82	1
8 [b]	(*R*)-**6b** (72±2)	78, 88; 58; 42	62.5 (*S*)	-1.47	4 [f, g]

[a] Conditions: ligand-to-nickel ratio 1; 5 mmol of **1a** and 6 mmol of Grignard compound **2b**; 50 μmol of Ni. – [b] Ligands with lower enantiomeric purities. – [c] The yield is based on the amount of **1a** used. – [d] Carried out with 18 mmol of $MgBr_2$ added to the $NiCl_2$/phosphane mixture. – [e] $\sigma[\ln(R/S)] = 0.09$. – [f] 5 mmol of **2b** used. – [g] 4 mmol of **2b** used.

Comparing catalytic runs with Grignard compound **2b** and either vinyl chloride (**1b**) (Table 3) or vinyl bromide (**1a**) (Table 5), enhanced enantioselectivities are found in the absence of bromide anions. The magnitude of this salt effect on the ln(*R*/*S*) scale is comparable to that found by Consiglio in his investigation of the cross-coupling reaction leading to 2-phenylbutane[3]. The use of Grignard compound **2b** and vinyl chloride (**1b**) produces the most enantioselective catalyst system ever reported in this catalysis with nickel complexes[2] (cf. entry 2 in Table 3). The influence of high bromide concentrations in solution was investigated by a catalytic run using **1a** and **2b** together with an added excess of $MgBr_2$ (cf. entries 5 and 6 in Table 5 and entry 5 in Table 3). On the ln(*R*/*S*) scale, the observed enantioselectivity was only 43% of that obtained in the cross-coupling of Grignard compound **2b** and vinyl chloride (**1b**). Consiglio and Indolese used (1-phenylethyl)magnesium bromide (**2a**) and vinyl chloride (**1b**) in their investigation. This choice of starting compounds gives a high bromide concentration in solution from the beginning of the cross-coupling reaction, like in our experiment with added $MgBr_2$. On the basis of our results, we suppose that if the bromide concentration in solution depends on the extent of conversion, then so does the enantioselectivity of this cross-coupling reaction with P,N ligands. This is the case when (1-phenylethyl)magnesium chloride (**2b**) and vinyl bromide are used as starting compounds. This combination of starting compounds was not used by Consiglio and Indolese[7].

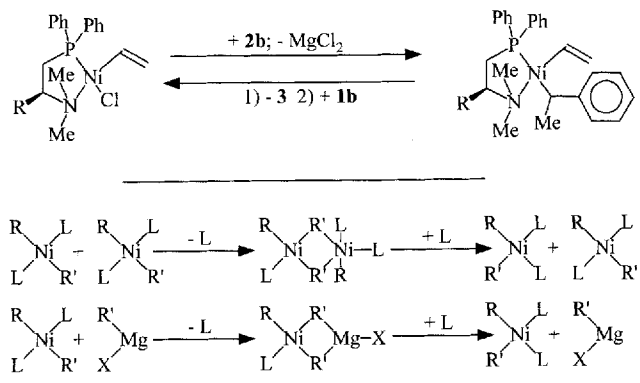
With nickel complexes of the secondary amine ligand (*R*)-**6** (cf. entries 1 in Tables 3–5; 6 mmol of Grignard compound **2b** used), only very low enantioselectivities and chemical yields can be attained. The amounts of phenylethane found in the hydrolysed reaction mixtures indicate that 4–5 mmol of **2b** is consumed.

In all reactions in Tables 3–5, small amounts of styrene (<2% of Grignard compound **2b** used) can be detected. It is formed by β-elimination of 1-phenylethyl groups coordinated to the nickel centre. It has been shown that $NiCl_2$ without added phosphane ligands can, in the presence of excess styrene, isomerise[4] a primary 2-phenylethyl Grignard compound to a secondary 1-phenylethyl Grignard compound[24]. We carried out several catalytic runs with nickel complexes of **6a**, with **6a**/Ni ratios equal to 1 or 2. In these experiments, (2-phenylethyl)magnesium bromide, vinyl halides **1a**, **1b** and excess styrene were used as starting materials. We could not detect any 3-phenyl-1-butene (**3**) formed by isomerisation of the primary 2-phenylethyl Grignard compound by GLC analysis of the products. The isomerisation of coordinated phenylethyl groups in catalytic runs with vinyl halides is a slow process compared to the cross-coupling reaction.

The Influence of the Ligand Structure on Enantioselectivity in P,N Monophosphane Catalysis

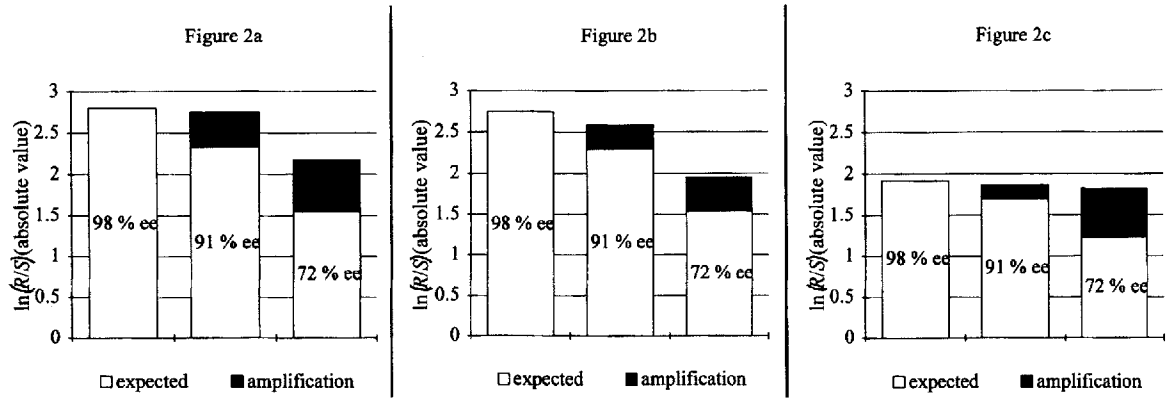
We compare here the catalytic results obtained with the ligands **6a–c** (cf. entries 2–4 in Table 5) with published results[2] obtained with P,N monophosphanes of type **4**. Both types of ligands have a β-aminoalkylphosphane skeleton. Complexes with the ligands (*S*)-**4b** [ln(*R*/*S*) = −2.25] and (*S*)-**4c** [ln(*R*/*S*) = −2.37; optical purity of ligand: 88% ee], bearing bulky substituents R on (*S*)-configured carbon centres in the β-position (cf. Scheme 1), are slightly more enantioselective than those with ligands (*R*)-**6a**, (*R*)-**6b**, or (*R*)-**6c** with (*R*)-configured carbon centres in the α-position, all the catalysts yielding (*S*)-**3** as the major enantiomer. It is generally accepted that the catalytic cycle of Grignard cross-coupling (cf. Scheme 2) involves oxidative addition of a vinyl halide to a nickel(0) complex, transmetallation from the Grignard compound and reductive elimination of 3-phenyl-1-butene (**3**) regenerating the nickel(0) complex[25].

Scheme 2. Collection of mechanistic schemes, suggested by Kumada and Kellogg[25] and in the lower part by Yamamoto[30]; details see text[a]



[a] X = halogen; L = monophosphane ligand; R, R′ = alkyl groups.

Figure 2. Nonlinear effects in catalytic runs with **6a**; the partition of experimental results into expected and amplification components is discussed in the text; in Figure 2a results with **6a**/Ni = 1, use of vinyl chloride (**1b**) are presented (cf. Table 3); in Figure 2b results with **6a**/Ni = 2, use of vinyl chloride (**1b**) are presented (cf. Table 4); in Figure 2c results with **6a**/Ni = 1, use of vinyl bromide (**1a**) are presented (cf. Table 5)



It is also generally assumed that 3-phenyl-1-butene (**3**) is eliminated from a complex in which a P,N phosphane acts as a chelating ligand[28]. A reductive elimination from this complex could be one reason for the high enantioselectivities observed in P,N monophosphane catalysis[16,25]. Noyori and coworkers have investigated the enantioselective addition of dialkylzinc compounds to benzaldehyde, as catalysed by chiral β-dialkylamino alcohol ligands[26]. These ligands also act as chelating N,O ligands for zinc in this catalysis. Ligands with either an (*R*)-configured carbon centre in the β-position or an (*S*)-configured carbon centre in the α-position yield the (*S*)-alcohol as the major product, in this case with comparable enantioselectivity.

Asymmetric Amplification

We find a positive, nonlinear relationship between the enantiomeric purities of the phosphane ligands **6a** or **6b** used and the enantiomeric purity of the cross-coupling product 3-phenyl-1-butene (**3**). The ln(*R*/*S*) values obtained with **6a** of 91% ee and 72% ee can be viewed as being composed of the expected contribution from the linear relationship supplemented by an amplification contribution (Figure 2).

Asymmetric amplification in catalytic runs with **2b** and vinyl chloride (**1b**) is influenced by the **6a**/Ni ratio (cf. Figure 2a to Figure 2b). We find that the amplification contribution decreases when a **6a**/Ni ratio of 2 is used. A similar comparison of the catalytic results obtained with **6b** of 94% ee and 72% ee (cf. Tables 3 and 4, entries 3, 7) reveaels the same trend. Catalytic results with (*S*)-**6c**/Ni ratios equal to 1, 2 or 3 (cf. entry 4 in Table 3 and entries 4, 8 in Table 4) further prove the influence of this ratio. Asymmetric amplification is also found to a similar extent in catalytic runs with **2b** and vinyl bromide (**1a**), (cf. Figure 2a to Figure 2c). For **6a** (91% ee purity), the amplification contribution in Figure 2c is small. In this context, it is worth mentioning that the bromide anion effect on enantioselectivity discussed earlier cannot be explained merely by a different extent of asymmetric amplification.

Asymmetric amplification is a novel, characteristic feature of the Grignard cross-coupling catalysis. Analysis of experimental data showing asymmetric amplification has been a valuable tool in assigning mechanisms[27]. Kagan and coworkers have provided a theoretical treatment of asymmetric amplification[28]. They show that asymmetric amplification can occur whenever diastereomeric catalysts of different reactivity are formed by coordination of at least two chiral ligands to transition metal centres or dinuclear associates. It is a general feature of catalysis with nickel monophosphane complexes[29] that many intermediate complexes with different NiL_n (n = 0–4) stoichiometries and free phosphanes (L) are present in solution during a catalytic run. Asymmetric induction in cross-coupling catalysis can arise either during reductive elimination or during transmetallation (cf. Scheme 2). Reductive elimination from Ni(II) complexes in which the alkyl groups are *cis*-oriented either proceeds in an unassisted manner or is induced by a fifth coordinated ligand[30,31]. Coordination of a second chiral phosphane ligand in this step, to yield diastereomeric intermediates or transition states, could be reason for the asymmetric amplification[28]. It is known that monophosphane complexes with *trans*-coordinated alkyl groups have to be isomerised by associative mechanisms to the *cis* complexes before reductive elimination can occur[30]. This *trans*-to-*cis* isomerisation can be promoted by the coordination of further phosphane ligands or by transmetallation steps. Two nickel complexes, or a nickel complex and a Grignard compound can associate, thus forming alkyl-bridged dimers (cf. Scheme 2). Coordinated enantiomers of the 1-phenylethyl group may be exchanged in this process. We suggest that the enhanced selectivity of monophosphane nickel catalysts compared to bisphosphane catalysts might be due to this *trans*-to-*cis* isomerisation step. This step is necessary in catalysis by monophosphane nickel catalysts because the thermodynamically more stable *trans*-coordinated nickel complexes are unable to undergo reductive elimination of the coupling products.

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Experimental Section

GC: Chrompack, model 438 A; FID (250°C); split injector (200°C), 70°C isotherm, 0.85 bar H_2 pressure. – FS-Cyclodex Beta-I/P® Phase II (60 m, 0.25 mm i.d., CS-Chromatography Service GmbH[21]). – Integration software Kontron Data System 450-MT2, V1.02.

Diethyl ether was dried and purified by distillation from $LiAlH_4$ and kept under argon. The new monophosphanes **6**, **6a–c** were prepared according to the procedure described in our recent paper[9]. The enantiomeric purity of ligands was assessed by polarimetry measurements, taking our published optical rotations as reference standards. All manipulations involving phosphanes and moisture-sensitive compounds were conducted under dry argon.

Synthesis of Grignard Compound **2b**: Magnesium turnings [Merck Schuchardt, "according to Grignard" quality] (26 g, 1.08 mol) were stirred dry and were subsequently covered with 80 ml of diethyl ether according to the procedure of Brown and coworkers[10]. The dropwise addition of 21.2 g (0.16 mol) of 1-phenylethyl chloride in 200 ml of diethyl ether at −10°C to 0°C often required up to eight hours due to problems in maintaining the stirring. The stirred mixture was stored at 0°C overnight and then filtered through Celite to remove precipitated $MgCl_2$. The resulting solution was made up to 400 ml and was stored for at least 4 days in a refrigerator. Then, a 10-ml aliquot was removed by syringe and hydrolysed in 20 ml of water containing 3 mmol of mesitylene. Further work-up was carried out as described for the work-up of catalytic runs (vide infra). GLC analysis was performed with a 1 µl sample of the resulting solution. From the relative integrals of mesitylene and phenylethane, the amount of stock solution used in catalytic runs could be calculated. On the basis of ten preparations of Grignard compound **2b**, we can state that at least 0.13 mol of **2b** could be used in catalytic runs.

Apparatus Used for Catalytic Runs: The glass reaction vessel was a Schlenk tube of 220 ml capacity equipped with a magnetic stirring bar (PTFE-coated). Instead of an NS 29 joint, the Schott screw cap system with a GL 32 (ISO) thread was used. Additionally, a PTFE valve (Winzer, 2.5 mm) was used instead of a stopcock system. In our experience, this system is more gas-tight than standard Schlenk equipment and avoids any problems that might be connected with the use of grease. In 200 catalytic runs (vide infra) only three had to be repeated because of leakage.

A 400-ml gas burette, filled with glycerol, was charged with vinyl chloride (**1b**) taken from a lecture bottle (Merck Schuchardt), fitted with a Monel needle valve. The glycerol was saturated with vinyl chloride for several weeks before the first catalysis was performed. A volume of 115 ml vinyl chloride (**1b**) was shown (using the second virial coefficient[32]) to equal 5 mmol. All flexible parts of the apparatus were made of PVC (reinforced with textile) tubings.

Catalytic Runs Using Vinyl Chloride (**1b**) *(in situ Catalysis):* To a 50 µmol sample of $NiCl_2$ was added a solution of 55 µmol (or multiples thereof, see Tables 3–5) of **6**, **6a–c** in 10 ml of diethyl ether and the mixture was stirred one hour. At −78°C, the Grignard solution (amount: see Tables) was added. The reactor was evacuated and sealed at the PTFE valve. It was then connected to the gas burette and all connecting tubing was evacuated. The gas burette was charged with vinyl chloride and sealed, and the connecting tubing was evacuated once more. Then, the vinyl chloride was completely condensed from the gas burette to the reactor. The reactor was again sealed and both reactor and the surrounding Dewar vessel, containing 100 ml of isopropanol and 50 g of dry-ice, were allowed to warm to room temperature overnight. The disonnected gas burette could be reused for further catalytic runs.

After 20 hours, the reactor was filled with Ar. An uptake of ca. 200 ml of Ar was necessary; if this was not the case some leakage had occurred and the catalytic run had to be repeated. Mesitylene (6 mmol) was added to the reaction mixture and then water (20 ml) was added slowly. Subsequently, aqueous HCl was added until all the solid components had dissolved and the aqueous phase became separated. It was extracted with several portions of diethyl ether. The collected diethyl ether phases were treated with K_2CO_3 and then filtered through Celite. The filtrate obtained was made up to 100 ml and was stored in a sealed bottle prior to GLC analysis. For GLC analysis, a 0.5–1-µl sample of this solution was injected.

Catalytic Run Using Vinyl Chloride (**1b**) *(Catalysis with Isolated $NiCl_2$ Complexes of* **5a**, **5b**): The synthesis of the known complexes[15] was performed according to the method of Brunner[16]. A 50-µmol sample of the complex was suspended in 10 ml of diethyl ether and the catalysis was carried out as before.

Catalytic Run Using Vinyl Bromide (**1a**): A reaction mixture containing the $NiCl_2$ phosphane mixture and the Grignard compound **2b** was prepared as before. The evacuated reactor was again filled with Ar, and 10 ml of diethyl ether containing 553 mg (5 mmol) of **1a** (Janssen) was added via a syringe. The reactor was evacuated and sealed once more. The subsequent reaction and work-up was performed as described for catalytic runs using **1b**.

X-ray Structure Determination of $C_{24}H_{38}MgO_2$ (**2b**): M = 382.85 g mol^{-1}, $d_{calcd.}$ = 1.114 g cm^{-3}, a = 1415.9(5), b = 1016.6(3), c = 1668.0(4) pm, β = 108.03(2)°, space group $C2/c$ (No. 15), V = 2.283(1) nm^3, Z = 4. – Data collection: Siemens P4 diffractometer, Mo-K_α (λ = 71.073 pm), graphite monochromator, measuring temp. T = 173 K, crystal dimensions 0.47 × 0.23 × 0.10 mm, ω scan, 2Θ = 4–50° (±h, ±k, ±l), 6645 reflections measured, 2008 independent, 1536 observed [$I > 2\sigma(I)$], µ = 0.09 mm^{-1}, absorption correction with ψ-scan (ellipsoid model), transmission 0.718 (min)/0.827 (max.). – Structure analysis and refinement: program SHELXTL V5.03[33], solution with Patterson method, full-matrix refinement, all non-hydrogen atoms were refined anisotropically, hydrogen atoms in calculated positions (riding model), 124 parameters, F_o/parameter = 12.39, $R1$ = 0.0313, $wR2$ = 0.0788, $Goof$ = 1.435. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Leopoldshafen-Eggenstein, Germany, on quoting the depository number CSD-405967, file-ID Ned-17, formula $C_{24}H_{38}MgO_2$.

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