# ASYMMETRIC NICKEL CATALYSIS IN THE CROSS-COUPLING REACTION OF ARYL HALIDES WITH GRIGNARD REAGENTS. A STUDY OF THE FACTORS INFLUENCING ASYMMETRIC INDUCTION

GIAMBATTISTA CONSIGLIO*, FRANCO MORANDINI† and ORESTE PICCOLO‡

Department of Industrial and Engineering Chemistry, Swiss Federal Institute of Technology, 8092 Zurich, Switzerland

**Abstract**—The synthesis of optically active 2-phenylbutane starting from phenyl halides and sec-butyl magnesium halides using nickel dichloro complexes of chiral homologues of 1,2-ethanediylbis[diphenylphosphine] has been investigated as a model cross-coupling reaction. Optical purities of up to 50% were obtained with little influence of the substituent(s) on the chiral ligand. By contrast the nature of the halide present in both the organic and the organometallic species is very important, leading to different optical purities and reversal of chiral discrimination. The nature of the ether solvent also modifies the optical yield; this influence, however, is not related to the basicity of the solvent. When the substrate is a substituted phenyl halide, the asymmetric induction seems to be strongly influenced by steric factors, but only slightly by electronic factors. The results suggest that there is a very complex mechanistic pathway for the catalyzed cross-coupling reaction and that the most important factor for the stereochemical course of the reaction is the structure of the alkylating organomagnesium species. Furthermore, the extent of the formation of isomeric alkylation products seems to be related to the stability of the metal containing chelate ring in the catalytic species.

Asymmetric cross-coupling of aryl and vinyl halides with chiral sec-alkylmagnesium halides catalyzed by nickel–chiral phosphine complexes[1] is a useful asymmetric carbon–carbon bond forming synthesis.[2–4] Efforts have been mainly directed towards finding optically active ligands which are able to exert a large asymmetric bias for a single reaction, namely for coupling vinyl bromide with 1-phenylethyl magnesium chloride.[5–10] Indeed, asymmetric induction as high as 94% was reported for the formation of 3-phenyl-1-butene from the above reagents using a nickel complex of (−)(R) - 1 - dimethylamino - 1 - t - butyl - 2 - diphenylphosphino - ethane as the chiral catalyst precursor.[6]

In view of the potential synthetic utility of the cross-coupling reaction, e.g. for the synthesis of essential oils,[11–13] we resumed our investigation in order to identify better the factors which control asymmetric induction and to extend the scope of the reaction. Nickel(II)dichloro complexes (2a–f) of chiral homologues of 1,2-ethanediylbis[diphenylphosphine] (1a–f)[14–19] (Chart 1), have been used as the asymmetric catalyst. Some results obtained using 2a have already been presented in a short preliminary communication.[20]

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†Present address: CNR, Centro di Studio sulla Stabilità e Reattività dei Composti di Cordinazione, Istituto di Chimica Analitica, Via Marzolo 1, Padova, Italy.

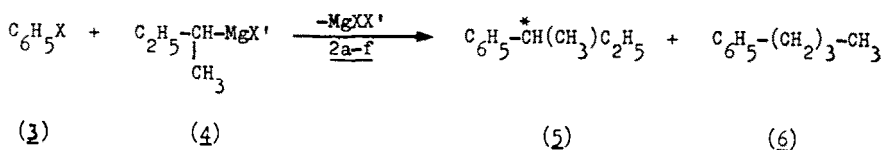‡Present address: Blaschim S.P.A. 20050 Peregallo di Lesmo, Italy.

## RESULTS
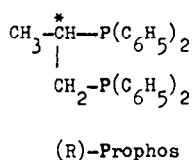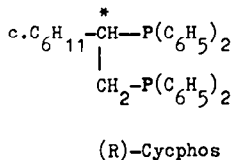
We have selected as the model reaction the synthesis of optically active 2-phenylbutane starting with sec-butylmagnesium halides and halogenobenzenes (Scheme 1) using the complexes 2a–f as the catalyst presursors.

Since the asymmetric cross-coupling reaction starting with chiral sec-alkylmagnesium compound has been described as a kinetic resolution with respect to this reagent,[10] we first examined the influence of increasing the ratio of sec-butylmagnesium bromide to bromobenzene on the optical yield in the formation of 2-phenylbutane (Table 1). These experiments have been carried out by maintaining a constant concentration of the Grignard reagent in order to ensure the presence of the same alkylating species. Indeed the association equilibrium of alkylmagnesium bromides depends on their concentration.[21] The optical yield decreases when higher amounts of Grignard reagents are used.

The influence of the dilution and the type of ether solvent on the optical yield in the cross-coupling between $C_6H_5X$ and sec-$C_4H_9MgX$ (where X is either Cl or Br) is shown in Table 2. In both cases the dilution brings about a decrease in the optical yield of the coupling product. No definite trend was observed when basicity of the ether solvent (THF or 'BuOMe vs Et$_2$O) was changed. In 'BuOMe the prevailing chirality of the alkylation production is opposite to that of the other cases; the use of THF causes a decrease of the optical yield when X=Br and an increase when X=Cl.

$$C_6H_5X \ + \ C_2H_5-\underset{\underset{CH_3}{|}}{CH}-MgX' \ \xrightarrow[\underline{2a-f}]{-MgXX'} \ C_6H_5-\overset{*}{CH}(CH_3)C_2H_5 \ + \ C_6H_5-(CH_2)_3-CH_3$$

$$(\underline{3}) \qquad\qquad (\underline{4}) \qquad\qquad\qquad\qquad (\underline{5}) \qquad\qquad (\underline{6})$$

Scheme 1.

CH$_3$–*CH–P(C$_6$H$_5$)$_2$
       |
       CH$_2$–P(C$_6$H$_5$)$_2$

(R)-Prophos

**1a**

c.C$_6$H$_{11}$–*CH–P(C$_6$H$_5$)$_2$
         |
         CH$_2$–P(C$_6$H$_5$)$_2$

(R)-Cycphos

**1b**

C$_6$H$_5$*CH–P(C$_6$H$_5$)$_2$
        |
        CH$_2$–P(C$_6$H$_5$)$_2$

(R)-Phephos

**1c**

CH$_3$–*CH–P(C$_6$H$_5$)$_2$
       |
       CH$_3$–*CH–P(C$_6$H$_5$)$_2$

(S,S)-Chiraphos

**1d**

P(C$_6$H$_5$)$_2$
···P(C$_6$H$_5$)$_2$

(R,R)-Norphos

**1e**

CH$_2$–*P(C$_6$H$_5$)(O–CH$_3$OC$_6$H$_4$)
       |
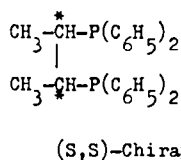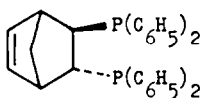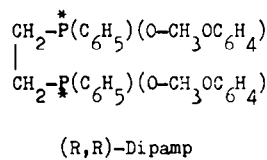       CH$_2$–*P(C$_6$H$_5$)(O–CH$_3$OC$_6$H$_4$)

(R,R)-Dipamp
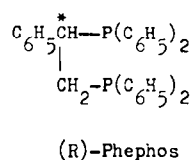
**1f**

Chiral catalyst precursors (L–L)NiCl$_2$ (**2a–f**): Structure of L–L (**1a–f**)

Chart 1.

Table 1. Cross-coupling reaction between PhBr and ˢBuMgBr in the presence of **2a**. Influence of the molar ratio of ˢBuMgBr to PhBr[a]

| sec-C$_4$H$_9$MgBr / C$_6$H$_5$Br molar ratio | Reaction time (hrs) | C$_6$H$_5$Br Conversion (%) | Alkylation products isolated yield %[b] | Isomerization %[c] | 2-Phenylbutane Optical purity (%) and absolute configuration[d] |
|---|---|---|---|---|---|
| 0.7 | 18 | 66 | 40 | 5.5 | 37.8 (R) |
| 1.3 | 23 | ~100 | 85 | 5.0 | 39.9 (R) |
| 3.3 | 24 | >98 | 80 | 5.0 | 33.3 (R) |
| 6.6 | 24 | >98 | 80 | 5.0 | 31.2 (R) |
| 10.0 | 23 | 85 | 65 | 5.5 | 29.5 (R) |

[a]RMgBr = 1.2 M in diethylether, C$_6$H$_5$Br=25 mmoles, molar ratio C$_6$H$_5$Br/**2a** = 300; [b]refers to the sum of (**5**) and (**6**) (Scheme 1); [c]percent of (**6**) with respect to the sum of (**5**) and (**6**); [d]calculated assuming $[\alpha]_D^{25}$ + 29.26 (neat) as the rotatory power of optically pure (S)-2-phenylbutane (Lardicci,L., Menicagli, R. , Atti Soc. Tosc. Sc. Nat., Mem., Ser.A, 1970,**77**,25).

Organomagnesium species containing alkoxy groups (which could form due to inadvertent exposure to air) can modify the optical yield in the cross-coupling reactions (Table 3). Such species were generated by partially destroying the Grignard reagent with ˢBuOH. In the presence of increasing amounts of ˢBuOMgX increased asymmetric induction was found, both when X=Cl or Br. Curiously, the same increasing quantities of alkoxy groups cause similar variation of the activation energy differences responsible for asymmetric induction in both cases.

Some of the results shown in the Tables 2 and 3 clearly show the effect on the optical yield of the type of halogen present in both moieties to be coupled. We shortly referred to this effect in the formation of 2-phenyl-butane using **2a** as the catalyst precursor.[20] Such an effect appears to be quite general, independent of the

chiral ligand used, as shown in Table 4. The absolute configuration of 2-phenylbutane is always the same as that of the chiral ligand. The reverse absolute configuration reported in the case of **2a** for X=X′=Cl[20] was due to the presence of some MgI$_2$ formed by iodine activation of magnesium for the preparation of the Grignard reagent[22] (*vide infra*). The reaction product obtained when **2f** is the catalyst precursor has very low optical purity For the other catalyst precursors asymmetric induction is larger when X=X′=Br than when X=X′=Cl. **2e** bringing about the highest extent of asymmetric induction. For the catalyst precursors **2a–d**, the extent of asymmetric induction has little dependence on the number and size of the substituents on the two carbon atom moiety between the phosphorus atoms.

However, the number and the size of the substituent influence the extent of the formation of the isomeric

Table 2. Cross-coupling reaction between PhX and $^s$BuMgX in the presence of **2a**. Influence of solvent

| Solvent | X = Cl | | X = Br | |
|---|---|---|---|---|
| | Isomerization (%)[c] | (5) Optical purity (%) and absolute configuration[d] | Isomerization (%)[c] | (5) Optical purity (%) and absolute configuration[d] |
| $Et_2O$ | 3 | 14.4 (R) | 5 | 39.9 (R) |
| $Et_2O$[b] | 3 | 6.0 (R) | 4 | 14.7 (R) |
| $t.C_4H_9OCH_3$ | ~1 | 0.8 (S) | 3 | 17.7 (S) |
| THF | ~1 | 20.4 (R) | 4 | 8.6 (R) |

[a] RMgX = 1.2 M unless otherwise stated, RMgX/C$_6$H$_5$X=molar ratio 1.3, C$_6$H$_5$X/**2a** molar ratio ≅300;
[b] RMgX = 0.12 M; Molar ratios between reagents and catalyst are the same as in the other cases;
[c,d] see same footnotes in Table 1.

Table 3. Cross-coupling reaction between PhX and $^s$BuMgX in diethyl ether catalyzed by **2a**. Influence of $^s$BuOMgX[a]

| $\dfrac{ROMgX}{RMgX}$ [b] | X = Cl | | X = Br | |
|---|---|---|---|---|
| | Isomerization (%)[c] | (5) Optical purity (%) and absolute configuration[d] | Isomerization (%)[c] | (5) Optical purity (%) and absolute configuration[d] |
| 0 | 3 | 14.4 (R) | 5 | 39.9 (R) |
| 0.18 | 3 | 20.7 (R) | 4 | 43.4 (R) |
| 0.74 | 2 | 24.1 (R) | 5 | 47.1 (R) |

[a] Same reaction conditions as in Table 2; [b] molar ratio; [c,d] see same footnotes in Table 1.

Table 4. Cross-coupling reaction of $^s$BuMgX with PhX catalyzed by **2**[a]

| Catalyst Precursor | X = Cl | | X = Br | |
|---|---|---|---|---|
| | Isomerization (%)[b] | Optical purity (%) and absolute configuration[c] | Isomerization (%)[b] | Optical purity (%) and absolute configuration[c] |
| **2a** | 3 | 14.4 (R) | 3 | 39.9 (R) |
| **2b** | <1 | 14.4 (R) | 4 | 45.8 (R) |
| **2c** | <1 | 18.5 (R) | 3 | 50.0 (R) |
| **2d** | <1 | 14.5 (S) | <1 | 43.1 (S) |
| **2e** | 10 | 26.7 (R) | 12 | 50.7 (R) |
| **2f** | 3 | 4.5 (R) | 10 | 4.2 (R) |

[a] Same reaction conditions as in Table 2; [b] see footnote c in Table 1; [c] see footnote d in Table 1.

cross-coupling product; the highest extent of isomerization is found for **2e**; the lowest for **2d**.

It is to be noted that in the cross-coupling reaction between PhI and $^s$BuMgI in the presence of **2a**, 2-phenylbutane having the same absolute configuration (R) as in the case of the corresponding chlorides (Table 4) and 21.1% optical purity is formed.[20] On the basis of

these results the effect of a small amount of $MgI_2$, particularly on the system in which X=X'=Cl is very surprising (Table 5). The prevailing absolute configuration of 2-phenylbutane is reversed (the optical purity remaining about the same) by about 1% of $MgI_2$ with respect to the two reagents to be coupled; larger quantities of $MgI_2$ (~3%) still cause an improvement of the

Table 5. Cross-coupling reaction between PhX and sec-$^s$BuMgX in diethyl ether catalyzed by **2a-b**. Influence of MgI$_2$

| Catalyst Precursor | X = Cl | | | X = Br | | |
|---|---|---|---|---|---|---|
| | $\dfrac{MgI_2}{RMgX}$ [b] | Isomeriza-tion (%) [c] | (5) Optical purity (%) and absolute configuration [d] | $\dfrac{MgI_2}{RMgX}$ [b] | Isomeriza-tion (%) [c] | (5) Optical purity (%) and absolute configuration [d] |
| 2a | 0 | 3 | 14.4 (R) | 0 | 5 | 39.9 (R) |
| 2a | 0.007 | 3 | 16.9 (S) | 0.01 | 5 | 41.8 (R) |
| 2a | 0.03 | 3 | 26.3 (S) | 0.022 | 5 | 44.5 (R) |
| 2b | 0 | <1 | 14.4 (R) | 0 | 4 | 45.8 (R) |
| 2b | n.d. | <1 | 5.4 (S) | n.d. | 4 | 47.2 (R) |

[a] Same reaction conditions as in Table 2; [b] molar ratio; [c,d] see same footnote in Table 1.

optical yield. Improvement in the optical yield is also observed for X=Br, but to a smaller extent than for X=Cl and without change in the prevailing absolute configuration of the 2-phenylbutane formed.

The study of the influence of the halogen has been extended to a cross-coupling reaction of $^s$BuMgX with other aromatic halides (Table 6). In each case we have obtained different optical yields and sometimes also different absolute configuration of the products depending on the halides. It is to be noted that in the case of o-halogenotoluenes and 1-halogenonaphthalenes optical yields are lower than in analogous cases and that in the series of the para-substituted phenylbromides products having the same absolute configuration and very similar optical purities were recovered (Table 6). Heteroaromatic compounds do not give much asymmetric induction and in the case of thiophene derivatives also very poor chemical yields were obtained.

### DISCUSSION

The possible mechanisms of the nickel catalysis in the cross-coupling reaction of Grignard reagents with vinyl- or arylhalides have recently been discussed.[23] Essential steps in all the proposed mechanisms are: (a) the activation of the Grignard reagent, leading to the formation of a nickel-alkyl-complex; (b) activation of the phenyl- or vinylhalide, leading to the formation of a Ni-C$_{sp2}$ $\sigma$-bond; (c) reductive elimination of the two organic moieties bound to nickel.

Controversy exists about the nature of the species which are responsible and about the order of activation of the organic and metallorganic reagents (Scheme 2, A and B). Particularly for step (c), assistance by the organic halide or by the organometallic species appears possible.[23]

The formation of optically active cross-coupling products in the alkylation of phenyl- or vinylhalides with sec-alkylmagnesium halides in the presence of chiral nickel complexes has been proposed to arise from a kinetic resolution of the Grignard reagent, which however should always exist in a racemic form since its inversion rate should be high in comparison with the rate of the coupling reaction. Indeed, the alkylation of the chiral nickel species by the organomagnesium compound should proceed with a different rate for each enantiomer. However, in the cross-coupling reaction between PhBr and $^s$BuMgBr, under such conditions that the same organomagnesium species should be present in solution (i.e. at the same concentration of the Grignard reagent),[21] an increase of the molar ratio of the Grignard reagent to PhBr (and to the catalyst) surprisingly does not improve or even maintain the constant extent of the optical yield. Rather, a small decrease in the extent of the asymmetric induction is observed. Since sec-alkylmagnesium chlorides should racemize with a higher rate than the corresponding bromides,[24] also in this case the inversion rate at the carbon atom bound to magnesium should not affect asymmetric induction. On this basis the alkylation of the chiral nickel intermediate by the Grignard reagent should be stereoselective.[25] However also a stereospecific alkylation followed by a rapid epimerization at the secondary carbon atom bound to the nickel, would
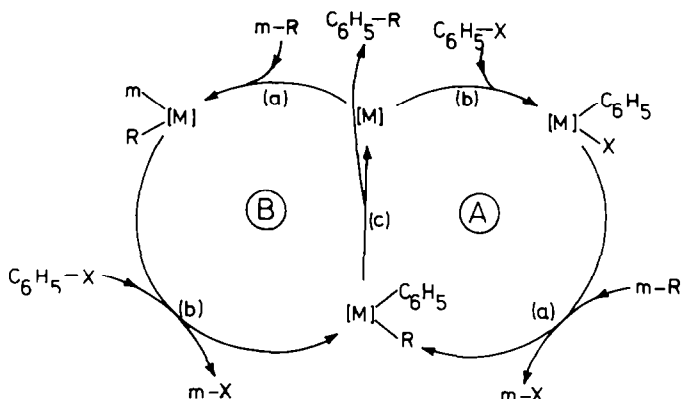


Scheme 2. Possible mechanisms for the nickel catalyzed cross-coupling reaction. [M] = Nickel atom with ancillary ligands; m = − MgX.

result in an optical yield which would be independent of the racemization rate. Unfortunately data on the stereochemistry of the transalkylation reaction of transition metal compounds by derivatives of the main group metal are rare and not conclusive.[26] However, since nickel catalyzed cross-coupling reactions are generally stereospecific[27, 28] we prefer the first alternative.

A decrease of the optical yield is observed with both halide systems when working in more diluted solution. When X=Cl, the association degree of the Grignard reagent should remain practically unchanged over a large concentration range.[21] Therefore an influence of the racemization rate on the optical yield under these conditions cannot be excluded, since racemization is known to require more than one molecule.[24] Such an effect (if it really exists) could also cause the decrease of the optical yield when X=Br. In this last case, however, the possible change of the structure of the organomagnesium compounds responsible for alkylation must be considered.

An increase in the basicity of the ether solvent should result in a decrease in the racemization rate of the Grignard reagents.[24] The results obtained in THF or in BuOMe, again, cannot be rationalized on this basis. A higher optical yield has been obtained using THF when X=Cl. On the other hand, the use of 'BuOMe causes very low optical yields and a change of the prevailing absolute configuration for both X=Cl and Br. This shows the large influence of solvation of the organometallic species responsible for alkylation of the catalytic species. Also solvation of the chiral reaction intermediates could play an important role. The effect of the presence of alkoxygroups and of magnesium iodide in the solution of the Grignard reagent can be also understood in terms of a modification of the structure of the organomagnesium species[21, 29] or of the catalytic species.

In the presence of MgI$_2$ different associates should form from RMgX(X=Cl or Br) which contain both halides and which could be the alkylating species. However the presence of MgI$_2$ could cause other competitive reactions. It has indeed recently been shown that nickel compounds catalyze redistribution of halogen atoms between aromatic halides and inorganic halides.[30] 'BuMgCl and 'BuMgI react with PhCl to produce 2-phenylbutane with prevailing (R)-configuration; PhI gives prevailing (S)-configuration with 'BuMgCl. The change of the absolute configuration in the products obtained in the cross-coupling of PhCl and 'BuMgCl in the presence or in the absence of MgI$_2$ could therefore be produced by a combination of the reactions shown in the Scheme 3. However we never observed formation of aromatic halides that were different from the starting materials.

The effect of MgI$_2$ on the optical yield in the formation of the cross-coupling products appears quite general, thus causing non-reproducible results when magnesium is activated by iodine[22] prior to preparation of the Grignard reagent. The direction of this effect can be different; in the alkylation of PhBr by 'BuMgBr the presence of MgI$_2$ brings about a higher asymmetric induction, whereas in the alkylation of 1- and 2-bromonaphthalenes the opposite is true.

The structure of the chiral ligand does not seem to have a great effect on the optical yield in the formation of 2-phenylbutane, particularly when 2a–d are the catalyst precursors. With these systems practically the same asymmetric induction was obtained when X=Cl, whereas only minor variations were observed when X=Br. To the contrary, when 1-dimethylamino-1-substituted-2-diphenylphosphino-ethanes were used as the chiral ligand,[6] the extent of the asymmetric induction strongly depended on the size of the substituent (e.g. ~30%

Table 6. Cross-coupling reaction between $^5$BuMgX and ArX in diethylether catalyzed by 2a. Influence of the halogen type, steric and electronic effects

| Ar — X | | RMgX X = | Reaction time (hrs) | Isolated yield (%)[b] | Isomeriza-tion (%)[c] | Chiral product[d] Optical purity (%) and absolute configuration |
|---|---|---|---|---|---|---|
| Ar | X | | | | | |
| $C_6H_5$ | Cl | Cl | 20 | 70 | 3 | 14.4 (R) |
| $C_6H_5$ | Br | Cl | 19 | 85 | 1 | 3.9 (R) |
| $C_6H_5$ | I | Cl | 3 | 80 | 3 | 14.9 (S) |
| $C_6H_5$ | Cl | Br | 10 | 70 | 3 | 22.3 (R) |
| $C_6H_5$ | Br | Br | 10 | 82 | 3 | 39.9 (R) |
| $C_6H_5$ | I | Br | 10 | 75 | 3 | 34.8 (R) |
| $C_6H_5$ | Cl | I | 24 | 80 | 4 | 4.1 (R) |
| $C_6H_5$ | Br | I | 24 | 78 | 5 | 32.7 (R) |
| $C_6H_5$ | I | I | 3 | 82 | 5 | 21.1 (R) |
| $o-CH_3C_6H_4$ | Cl | Cl | 20 | 75 | 1 | 9.5 (S) |
| $o-CH_3C_6H_4$ | Br | Br | 16 | 60 | 2 | 12.5 (S) |
| $m-CH_3C_6H_4$ | Br | Br | 24 | 75 | 7 | n.d.[e] |
| $p-CH_3C_6H_4$ | Br | Br | 24 | 66 | 8 | 36.0 (R) |

Table 6 (*Contd*).

| Ar - X | | RMgX X = | Reaction time (hrs) | Isolated yield (%) [b] | Isomerization (%) [c] | Chiral product Optical purity (%) and absolute configuration [d] |
|---|---|---|---|---|---|---|
| Ar | X | | | | | |
| $p\text{-}CH_3OC_6H_4$ | Br | Br | 4 | 84 | 10 | n.d.[f] (R)[g] |
| $p\text{-}(CH_3)_2NC_6H_4$ | Br | Br | 70 | 63 | 8 | 35.4 (R) |
| $p\text{-}CF_3C_6H_4$ | Br | Br | 72 | n.d. | 10 | 36.0 (R) |
| $p\text{-}CH_2\text{=}CHC_6H_4$ | Br | Br | 40 | n.d. | 4 | 36.0 (R) |
| $1\text{-}C_{10}H_7$ | Cl | Cl | 16 | 90 | ~0 | 5.5 (S) |
| $1\text{-}C_{10}H_7$ | Br | Br | 10 | 85 | ~0 | 7.7 (R) |
| $2\text{-}C_{10}H_7$ | Cl | Cl | 12 | 89 | 1 | 17.6 (R) |
| $2\text{-}C_{10}H_7$ | Br | Br | 12 | 90 | 1 | 47.7 (R) |
| $2\text{-}C_4H_3S$ | Br | Br | 3 | ~0[h] | - | - |
| $3\text{-}C_4H_3S$ | Br | Br | 21 | n.d. | 61 | 2.0 (S) |
| $2\text{-}C_5H_4N$[i] | Cl | Cl | 7 | 70 | ~0 | 1.6 (R) |
| $2\text{-}C_5H_4N$[i] | Br | Br | 12 | 80 | ~0 | 3.6 (S) |
| $3\text{-}C_5H_4N$[i] | Cl | Cl | 10 | 50 | ~0 | ~0 (R) |
| $3\text{-}C_5H_4N$[i] | Br | Br | 19 | 65 | ~0 | 16.4 (R) |
| $4\text{-}C_5H_4N$[i] | Cl | Cl | 24 | 85 | ~0 | 14.0 (R) |
| $4\text{-}C_5H_4N$[i] | Br | Br | 24 | 80 | ~0 | 3.0 (R) |

[a]Reaction conditions as in Table 2, unless otherwise stated; [b,c]see corresponding footnotes in Table 1; [d]data calculated on the basis of the following maximum rotatory powers, which correspond to products having (S) absolute configuration: 2-phenyl-butane,$[\alpha]_D^{25}$ + 29.26 (neat) ( Lardicci,L., Menicagli, R., Atti Soc.Tosc.Sc.Nat.Mem.A, 1970, 77, 25 ); 2-o.tolylbutane, $\alpha_D^{25}$ + 28.59°( l = 1, neat) ( present work ); 2-p.tolylbutane,$[\alpha]_D^{25}$ + 30.3 (c= 0.032, methanol) ( Verbit, L., Rao, A.S., Clark-Lewis, J.W., Tetrahedron, 1968, 24, 5839 ); 2-(p.dimethylamino)-phenylbutane,$[\alpha]_{436}^{25}$+ 83.6 (c= 0.39, carbon tetrachloride) ( present work ); 2-(p.trifluoromethyl)phenyl-butane,$[\alpha]_D^{22}$+ 20.9 (c= 5,benzene) ( Capillon, J., Guetté, J.P.,Tetrahedron 1979, 35, 1807 ); 2-p.styryl-butane, $[\alpha]_D^{25}$ + 46.17 (neat) (elaborated on the basis of data of optical purities of compounds reported in Ciardelli, F.,Pieroni, O., Carlini, C., Menicagli, C.,J.Polym.Sci.Polym.Chem. Ed. 1972, 10, 809 and Menicagli, R., Piccolo, O.,J.Org.Chem. 1980, 45, 2581 ); 2-(1-naphtyl)butane,$[\alpha]_D^{25}$+ 25.43 (neat) and 2-(2-naphtyl)butane,$[\alpha]_D^{25}$ + 30.22 (neat) ( Menicagli,R., Piccolo, O., Lardicci, L., Wis, M.L.,Tetrahedron, 1979, 35, 1301);2(3-thyenyl) butane, $[\alpha]_D^{25}$+ 38.86 (c= 3.49, n-heptane) (Botteghi, C., Lardicci, L., Menicagli, R.,J.Org.Chem. 1973, 38, 2361 ); 2-(2-pyridyl)butane, $[\alpha]_D^{25}$ : 39.95 (neat), 2-(3-pyridyl)butane, $[\alpha]_D^{25}$ + 44.50 (neat) and 2-(4-pyridyl)butane, $[\alpha]_D^{25}$ (c= 2.29, n-heptane)(Tatone,D., Dich, T.C., Nacco, R., Botteghi, C.,J.Org.Chem. 1975,40, 2987); [e]$[\alpha]_D^{25}$ - 11.15 (c= 3.372, benzene); [f]$[\alpha]_D^{25}$ -90.38 (c= 2.364, benzene); [g]Spenninger, P.A., von Rosenberg, J.L., Chem.Comm. 1970,795 and present work; [h]thiophene was obtained almost quantitatively ; [i]the Grignard reagent was added at 0°C and the reaction mixture was then maintained at room temperature.

for Me, ~70% for Ph, ~94% for 'Bu) at least in the coupling reaction between $C_6H_5\text{-}CH(CH_3)MgCl$ and $CH_2\text{=}CHBr$.

The minimum influence of the structure of 2a–d on the optical yield and the fact that 2e causes the highest asymmetric induction but 2f a very low one can be interpreted by assuming that the factor mainly responsible for the stereochemical course of the cross-coupling reaction is the chiral conformation of the chelate ring in the catalytic species.[14,17] Such conformation would be forced by the substituent(s) in the ring (Fig. 1). Therefore the size of the substituent on the chiral center in the
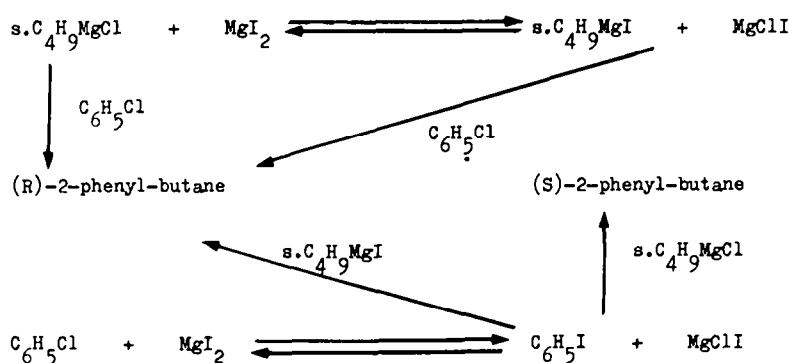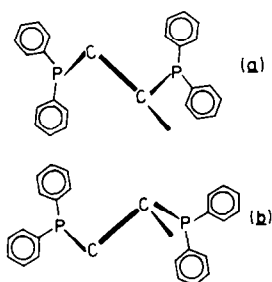
Scheme 3.



Fig. 1. Preferred conformations for a mono-substituted coordinated 1,2-ethanediyl[diphenylphosphine] having (S)-(a) or (R)-configuration (b).

ligands 2a–d should play a secondary role, at least in this case. However, when 2f is the chiral ligand, the possibility exists of transforming the chiral ligand in an achiral one. Indeed, it has been shown that reversible oxidative addition to P–C bonds to nickel(0) complexes can take place.[31] Such reaction involving the o-methoxyphenyl substituent followed by metathesis with phenyl groups would destroy the chirality at the phosphorus, thus causing a very low extent of asymmetric induction.

In the alkylation of the three isomeric tolylbromides the 2-(m-) and 2-(p-tolyl)butanes recovered had the same absolute configuration (R) and about the same optical purity of 2-phenyl-butane obtained under the same reaction conditions. To the contrary, o-methyl-2-phenyl-butane has the opposite absolute configuration, the optical purity being 12.5%. Analogously, 2-bromo-naphthalene is alkylated with $^sBuMgBr$ in the presence of 2a with much higher asymmetric induction ($\sim 48\%$) than 1-bromonaphthalene ($\sim 8\%$). Thus apparently for more hindered phenyl derivatives, when 2a is used as the catalyst precursor, formation of the (S)-enantiomeric alkylation product appears more favoured.

If we consider that p-substituted phenylbromides give alkylation products with enantiomeric excesses similar to those obtained with phenylbromide independent of the nature of the substituent, we are compelled to assume that charge-transfer processes[23] leading to species of the type $L_nNiAr(sec.\ C_4H_9)^+ArBr^-$, even if they exist, are not important for the stereochemical course of the alkylation reaction.

The comparison of the results obtained for phenyl halides with those for the isomeric pyridine halides suggests that in the latter case possible interactions of the nitrogen atom with the Grignard reagent and/or with the
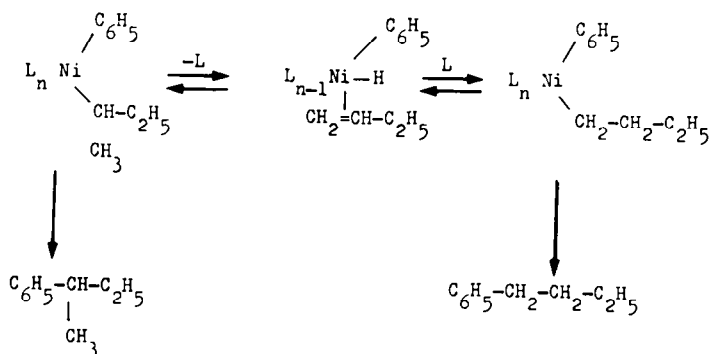
nickel species and concurrence of the non-catalyzed cross-coupling reaction (that could occur to some extent particularly with the 2- and the 4-bromo derivative) can cause the lack of regularity in the trend of the asymmetric induction.

## CONCLUSIONS

The results reported in this paper show that the optical yield in the synthetically useful cross-coupling reaction is influenced by different reaction parameters that are not easily rationalized, particularly due to the uncertainty concerning the nature of the catalytic species and to the order of activation of the two moieties to be coupled. Kinetic studies of this reaction are hampered by the fact that the catalyst is somewhat destroyed during the reaction. However, we feel that the major factor which determines the optical yield is the structure of the organometallic species responsible for alkylation of the nickel catalyst. Furthermore, the decrease of the optical yield observed when the sec-$C_4H_9MgBr$ to $C_6H_5Br$ molar ratio is increased cannot be explained by simple mechanisms consisting of sequences of steps c–b–a or c–a–b[23] (Scheme 2). Either a competition between different mechanistic pathways or more complex catalytic species appear more probable.[23] Under such species, complexes containing the ligands in a monodentate fashion could also exist. This aspect seems to be very important as far as the formation of isomeric cross-coupling product is concerned. Model studies indicate that the formation of such products proceeds through dissociation of one phosphorous ligand (Scheme 4).[23] We have observed that the order of the (at least kinetic) stability of the species containing that ligands dpe, 1a and 1d in a monodentate fashion is dpe > 1a > 1d in the displacement reaction of $PPh_3$ by the above ligands from $(\eta^5\text{-}C_5H_5)RuCl(PPh_3)_2$.[32] In the cross-coupling reaction (1) (e.g. for X=X'=Cl) catalyzed by $NiCl_2(dpe)$, 2a and 2d the amount of isomeric alkylation product are 9%, 3% and < 1% respectively. Furthermore the higher extent of isomerization observed in the case of 1e could be a consequence of a certain stability of such a ligand bonded in a monodentate fashion because of the severe distortion caused by chelation.[33] Finally, the importance of steric factors with respect to electronic ones in influencing the optical yields should be stressed.

$$L_n Ni \underset{\ce{CH-C_2H_5}}{\overset{C_6H_5}{\diagup}} \underset{\ce{CH_3}}{\overset{}{}} \xrightleftharpoons[]{-L} L_{n-1} Ni-H \underset{\ce{CH_2=CH-C_2H_5}}{\overset{C_6H_5}{\diagup}} \xrightleftharpoons[]{L} L_n Ni \underset{\ce{CH_2-CH_2-C_2H_5}}{\overset{C_6H_5}{\diagup}}$$

$$C_6H_5-CH-C_2H_5 \atop CH_3 \qquad\qquad\qquad C_6H_5-CH_2-CH_2-C_2H_5$$

Scheme 4.

Sigma 4 with flame ionization detectors. Preparative GCs were carried out on a Perkin–Elmer F21 using 3 or 5 columns 90 × 0.95 cm packed with 20% Silicone gum SE 52 on Chromosorb A 60–80 mesh or 8% Carbowax 20 M + 2% KOH on Chromosorb W. Optical rotations were measured with a Perkin Elmer Polarimeter 141. NMR spectra were recorded at 90 MHz on a WH 90 Bruker spectrometer using TMS as the internal standard. Mass spectra were run on a Hitachi/Perkin–Elmer RMU-GL spectrometer. Physical constants and spectroscopic data of the known compounds were consistent with those of the literature.

Chiral diphosphines **1a–d** were prepared by following the procedures described in the literature.[14–17] Nickel dichloro complexes **2a**, **2c** and **2d** were prepared as described elsewhere[14]; **2b**, **2e** and **2f** were similarly synthesized.

*General procedure for the cross-coupling reaction*

At room temp 65 mmole of the Grignard reagent in ether solution were added to an ether mixture of 50 mmole of arylhalide and 0.16–0.20 mmole of the catalyst precursor. The total volume of the reaction mixture was about 60 ml. The mixture was refluxed and then was hydrolyzed at 0°C with $H_2O$ and dil $H_2SO_4$. The coupling product was separated from the solvent by rotary evaporation and then fractionally distilled over $LiAlH_4$ in vacuo. If it was necessary for the determination of the optical rotation, the product was further purified through preparative GC.

In the case of the pyridine derivatives, the addition of the Grignard reagent was made at 0°C and the mixture was allowed to react at room temperature. The hydrolysis was carried out with water and the coupling product was extracted continuously with ether. Distillation of the product was made over KOH.

*Ozonolysis of 2-(o-tolyl)butane.* 3.0 g (20 mmole) of 2-(o-tolyl)butane having $\alpha_D^{25} + 3.145$ ($l = 1$, neat) were dissolved in 80 ml glacial acetic acid and a stream of ozonized $O_2$ was bubbled into the solution for 25 h, at room temp. The mixture was concentrated under reduced pressure (10 torr) and the residue, dissolved in 200 ml dry ethyl ether, was reduced with an ether suspension of 6 g (0.16 mol) $LiAlH_4$. The hydrolysis was accomplished as usual. After elimination of the solvent followed by preparative GC, a pure sample of (−)-2-methyl-1-butanol showing $[\alpha]_D^{25} - 0.735$ ($c = 3.95$, *n*-heptane) (op 11%)[35] was recovered.

*Ozonolysis of 2-(p-dimethylamino)phenylbutane.* 3.0 g (17 mmole) of 2-(p-dimethylamino)phenylbutane having $[\alpha]_{436}^{25} - 29.59$ ($c = 0.39$, carbon tetrachloride) were dissolved in 100 ml methylene chloride and a stream of ozonized $O_2$ was bubbled into the soln for 20 h at 0°C. The mixture was then treated as described above. GC purification afforded a pure sample of (+)-2-methyl-1-butanol having $[\alpha]_D^{25} + 2.36$ ($c = 4.05$, *n*-heptane) (op 35.4%).[35]

*Ozonolysis of 2-(p-methoxy)phenylbutane.* 2 g (12 mmole) of 2-(p-methoxy)phenyl-butane having $[\alpha]_D^{25} - 10.38$ ($c = 2.364$, benzene) were ozonized in 80 ml glacial acetic acid. The mixture was worked up as above to afford (+)-2-methyl-1-butanol. However, the amount of the alcohol recovered was too small for an accurate determination of its optical purity.

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