# Zinc Halide Induced Switch in Enantioselection in Nickel and Palladium Catalysed Cross Coupling Reactions

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The sense of stereoselection in the cross coupling of the Grignard reagent of 1-phenethyl chloride with vinyl bromide, catalysed by nickel or palladium complexed to ligands derived from amino acids, inverts on addition of anhydrous zinc bromide.

The cross coupling depicted in Scheme 1 serves as a model for investigation of catalytic asymmetric induction in the formation of carbon–carbon bonds.[1] Kumada and Hayaishi made the useful discovery that ligands (4), readily derivable from amino acids [(5), Scheme 2], induce quite reasonable enantiomeric excesses (e.e.s) of 3-phenylbut-1-ene (3).[2] We have shown that inclusion of an extra heteroatom in the side chain of the ligand, e.g. (4b and c), can provide still higher levels of enantioselection,[3] which is consistent with the presumed mechanism of the oxidative addition/reductive elimination cycle leading to (3).[4] For the fourteen derivatives of (4) [(4a—e) are a sample][2,3] the S (natural) configuration of the amino acid (5) used in ligand synthesis corresponds with the S configuration of (3) formed in excess. This suggests that a common, but as yet unidentified, structural feature determines the sense of enantioselection.

We find that this sense of enantioselection is effectively reversed on addition of certain zinc salts (See Table 1). Optical yields were determined on neat (3) isolated by preparative g.l.c. using $[\alpha]_D^{22}$ −5.91° for the optically pure R

enantiomer.[1a] A thermostatted polarimeter cell was used for measurement of rotation because the optical rotation of neat (3) is remarkably temperature dependent and increases linearly for enantiomerically pure material,[†] 0.18°/°C in the temperature range of 16—29 °C.

The reactions have high catalytic efficiencies. A ratio of reagent (2) to metal–ligand complex of $1:10^{-3}$ is used in all cases. Previously reported reactions have involved ratios no higher than $1:2.5 \times 10^{-2}$.[1—4][‡] Also, the addition of a stoicheiometric amount of $ZnBr_2$ leads to a clean reversal in the sense of enantioselection (compare runs 1 and 2; 5 and 6; 9 and 10; 11 and 12; and to a lesser extent 7 and 8 for nickel, and 13 and 14 for Pd) and to increased reactivity of the system (e.g. compare runs 3 and 4). Other additives like $MgBr_2$ (17 and 18) have no observable effect; $ZnI_2$ (not shown) is roughly as effective as $ZnBr_2$. $ZnCl_2$, on the other hand, has a pronounced inhibitory effect (runs 21 and 23).

**Scheme 1**

(5)                                            (4)
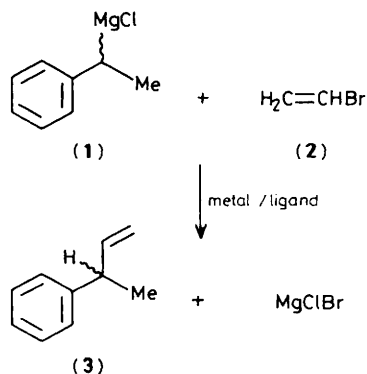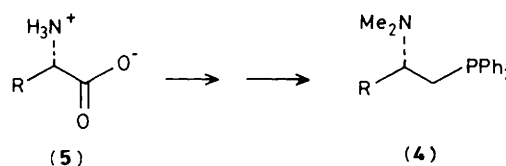
**Scheme 2.** a; R = Pr$^i$
b; R = $Me_2N(CH_2)_4$
c; R = $MeSCH_2$
d; R = $MeS(CH_2)_2$
e; R = $MeS(CH_2)_3$

† The change in rotation/°C slopes for three samples of (3) of different e.e.s were measured; the value for enantiomerically pure material was then derived from extrapolation of a plot of e.e. against slope.

‡ A consequence of these high turnovers is some deviation, either upwards or downwards, of the e.e.s reported here for the various ligands from previous observations.

**Table 1.** Ni and Pd catalysed cross coupling reactions.[a]

| Run | Metal/Ligand | $T/°C$ | $t/h$ | Additive | % Yield | $[\alpha]_D^{22}/°$ | % Opt. yield |
|---|---|---|---|---|---|---|---|
| 1 | Ni/(S)-(4e) | 0 | 21 | — | 95 | +3.60 | 61(S) |
| 2 | Ni/(S)-(4e) | 0 | 21 | ZnBr$_2$ | 71 | −3.95 | 67(R) |
| 3 | Ni/(S)-(4e) | −34 | 21 | — | 0.4 | — | — |
| 4 | Ni/(S)-(4e) | −34 | 21 | ZnBr$_2$ | 73 | −4.14 | 70(R) |
| 5 | Ni/(S)-(4d) | +4 | 96 | — | >95 | +3.52 | 60(S) |
| 6 | Ni/(S)-(4d) | +2 | 16 | ZnBr$_2$ | 88 | −3.08 | 52(R) |
| 7 | Ni/(R)-(4c)[b] | +1 | 30 | — | >95 | +2.15 | 36(S) |
| 8 | Ni/(R)-(4c)[b] | +6 | 30 | ZnBr$_2$ | >95 | −0.01 | 2(R) |
| 9 | Ni/(S)-(4b) | 0 | 12 | — | 83 | +2.75 | 47(S) |
| 10 | Ni/(S)-(4b) | 0 | 12 | ZnBr$_2$ | 83 | −2.67 | 45(R) |
| 11 | Ni/(S)-(4a) | 0 | 12 | — | >95 | +4.10 | 69(S) |
| 12 | Ni/(S)-(4a) | 0 | 12 | ZnBr$_2$ | <10 | −2.04 | 41(R) |
| 13 | Pd/(S)-(4d)[c] | +2 | 120 | — | >95 | +1.92 | 33(S) |
| 14 | Pd/(S)-(4d)[c] | +5 | 120 | ZnBr$_2$ | 12 | −1.00 | 17(R) |
| 15 | Pd/(S)-(4a)[c] | 0 | 120 | — | 86 | +1.87 | 32(S) |
| 16 | Pd/(S)-(4a)[c] | 0 | 120 | ZnBr$_2$ | <10 | — | — |
| 17 | Ni/(S)-(4e) | −1 | 60 | MgBr$_2$ | >95 | +3.49 | 59(S) |
| 18 | Ni/(S)-(4a) | −3 | 60 | MgBr$_2$ | >95 | +4.35 | 74(S) |
| 19 | Ni/(S)-(4e) | +4[d] | 96 | ZnBr$_2$ | nil | — | — |
| 20 | Ni/(S)-(4d) | 0[d] | 16 | ZnBr$_2$ | nil | — | — |
| 21 | Ni/(4a) | −4 | 80 | ZnCl$_2$ | nil | — | — |
| 22 | Ni/(4a) | 0 | 80 | ZnI$_2$ | 43 | −2.75 | 47(R) |
| 23 | Ni/(4e) | +3.5 | 16 | ZnCl$_2$ | nil | — | — |
| 24 | Ni/(4e) | −2 | 16 | ZnI$_2$ | 16 | −3.07 | 52(R) |

[a] Yields are based on vinyl bromide (12.5 mmol, 0.25 M in Et$_2$O); the ratio (1):(2):Ni (or Pd):(4) is in all cases 2:1:10$^{-3}$::10$^{-3}$. NiCl$_2$, (4), and vinyl bromide (2) were mixed in Et$_2$O and brought to −10 °C. The Grignard reagent (4) (0.7—0.9 M in Et$_2$O determined by titration) was added dropwise to the stirred solution. After addition was complete the solution was warmed to temperature $T$ and was allowed to stand for the indicated period. The reaction mixture was cooled to −20 °C and quenched with aqueous HCl. After work-up (3) was isolated by preparative g.l.c. The ratio of zinc halide to (2) was 2.5:1. [b] Derived from (S)-cysteine; the configurational symbol changes because of the Cahn–Ingold–Prelog rules. [c] Preformed complexes of PdCl$_2$/(2) were used. [d] The Grignard reagent was stirred with ZnBr$_2$ at room temperature for 1 h and was then cooled to −10 °C before addition to the catalyst mixture.

The involvement of organozinc reagents is unlikely. Runs 19 and 20 involve preformation of the zinc reagent by prior metathesis of ZnBr$_2$ with the Grignard reagent (1); the organometallic reagent derived from this treatment is totally unreactive towards the Ni$^0$/(4d) or (4e) complex (this experiment was also done with preformed Ni$^0$ complex to eliminate the possibility that the organozinc reagents are incapable of inducing formation of this catalytically active species).

The reactions with ligand (4a) (isopropyl side chain) in the presence of ZnBr$_2$ are sluggish compared to ligands (4b—e) that possess heteroatoms in the side chain (see runs 11, 12, 21, and 22). This suggests ligation of ZnBr$_2$ to the side chain as an integral component of the mechanism. However, the pronounced tendency of Zn$^{II}$ to form zincate anions with halide may also aid in activating the transition metal.[5] The increase in reactivity is far greater for the Ni than the Pd catalysed reactions as seen from, for example, comparison of entries 6 and 14. It is not clear at what stage in the oxidative addition/reductive elimination sequence that these effect occur. This reversal effect of ZnBr$_2$ on the absolute configuration of the product is reminiscent of the observations of Posner et al. on the copper catalysed addition of Grignard reagent to α,β-unsaturated sulphoxides in which zinc chelates are clearly involved.[6]

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