Chiral (Macrocyclic) Sulphides as Ligands for Nickel Catalysed Carbon–Carbon Bond Formation

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Various sulphide combinations have been synthesized and examined as ligands for the Ni^{II} catalysed cross coupling of α-phenylethylmagnesium chloride and vinyl bromide; good yields and, in some cases, modest enantiomeric excesses can be obtained.

Some transition metals catalyse the formation of carbon–carbon bonds by an oxidative-addition/reductive-elimination cycle.[1] The development of such transition metal catalysis depends largely on the availability of suitable ligating compounds. Up to now only chiral phosphines or phosphine–amine combinations have provided satisfactory results[2,3] for enantioselective carbon–carbon bond formation. This is a severe limitation for the synthesis of phosphines is not simple and the derived ligands, once obtained, are often sensitive, especially to oxidation by air.

These considerations induced us to investigate readily available chiral sulphides as potential ligands. The availability of a route to chiral macrocyclic sulphides[4] provided additional impetus. Sulphide complexes are likely to be more labile than those with phosphines, although the affinity of the sulphides for many transition metals is well established.[5]

The potential bi- and poly-dentate ligands (**1**)—(**5**) have been synthesized and tested. The syntheses are unexceptional. Starting materials are the cyclohexanone acetal of (*R*)-(+)-tartaric acid for (**1**), (2*S*,3*S*)-butane-2,3-dithiol for (**2**),[6] (*S*)-valine [*via* (*S*)-1-chloro-2-dimethylamino-3-methylbutane][7] for (**3**), and (*S*)-*S*-methylcysteine [*via* (*R*)-1-chloro-2-dimethylamino-3-methylthiopropane] for (**4**) and (**5**).

These ligands were tested on the Ni^{II} catalysed cross coupling of 1-phenylethylmagnesium chloride (**6**) with vinyl bromide (**7**) to give (**8**) as shown in equation (1). This reaction has been examined thoroughly by Consiglio[8] and Kumada.[3] Results are given in Table 1. The ratio (**6**) : (**7**) : $NiCl_2$: ligand was held constant at 0.8 : 1 : 0.005 : 0.005. The reaction was carried out in diethyl ether at -10 °C to 0 °C for 5 h. The chemical yield is based on (**6**).

Compound (**1**) appears to be a poor ligand. On the other hand ligands with sulphur separated by two [(**2**), (**5**)] or three

Table 1. Ni^{II} catalysed formation of 3-phenylbut-1-ene (**8**).

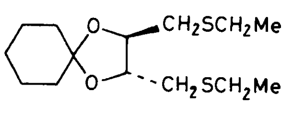
Ligand	Chemical yield, %	E.e., %	Configuration[a]
none	53[b]	[c]	[c]
(**1**)	53	—	—
(**2**)	90	0.8	(*R*)
(**3**)	81	—	—
(**4**)	90	4.3	(*R*)
(**5**)	78	7.7	(*S*)

[a] Maximum rotation of (**8**) taken as $[\alpha]_D^{22}$ +5.9° (neat) for (*S*) enantiomer. [b] After 40 h (instead of the usual 5 h) reaction time. Et_2O apparently solubilizes a small amount of $NiCl_2$, which induces a slow conversion into product. [c] Not applicable.

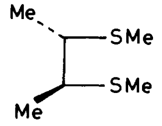
Table 2. Ligand (**9**) for Ni^{II} catalysed cross coupling.

Entry	Ratio reagents[a] (**9**)	NiCl$_2$	(**6**)	(**7**)	Temp./°C	Reaction time/h	Chemical yield (**8**)[b]	E.e.,%[c] (absolute configuration)
1	0.005	0.005	0.8	1.0	−10→0	5	87	8.1 (*S*)
2	0.005	0.005	0.8	1.0	−20	24	87	9.7 (*S*)
3	0.005	0.005	0.8	1.0	−70	24	72	5.0 (*S*)
4	0.02	0.002	0.8	1.0	−10→0	5	85	6.1 (*S*)
5	0.01	0.01	2.0	1.0	−10→0	24	100[d]	16.9 (*S*)

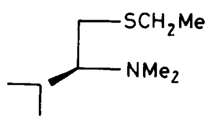
[a] Solvent Et_2O; concentration (**7**) 1 M. Reactions carried out under N_2 with magnetic stirring. [b] Calculated with (**6**) as limiting reagent. [c] Error estimated at ±0.4%. [d] Calculated with (**7**) as limiting reagent.



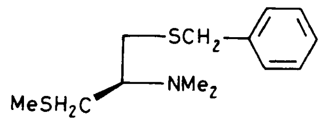
(**1**)



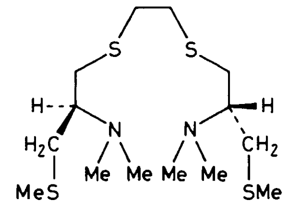
(**2**)



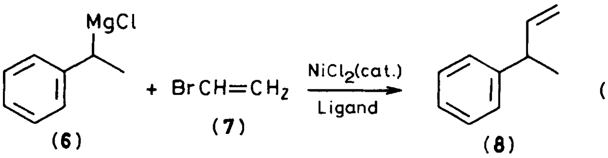
(**3**)



(**4**)



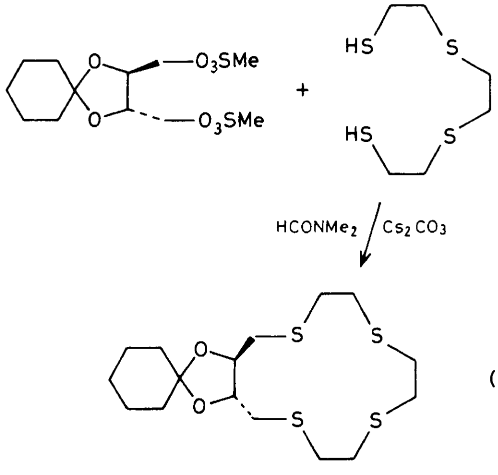
(**5**)



(1)

carbon atoms [(**4**)] clearly induce coupling. The enantiomeric excess (e.e.) with (**5**) is virtually the same as that obtained with (2*S*,3*S*)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (diop), which has a tartaric acid skeleton substituted with two diphenylphosphines.[8]

Increased rigidity of a good ligand should lead to increased e.e's in the coupling reaction. The macrocycle (**9**) was available to us as an extrapolation of previous work.[4,9] The critical step is the caesium promoted ring closure as shown in equation (2). Although the apparently poor design aspects of ligand (**1**) are present, we hoped that the extra sulphides would provide compensating ligand sites. Results for (**9**) as ligand in equation (1) are given in Table 2. The reaction is sensitive to temperature (entries 1—3). Additional ligand (entry 4) has a negligible effect. Use of excess of Grignard reagent, contrary to the observations of Consiglio,[10] leads to a higher e.e. (entry 5). The induction in this case is more than twice that obtained with diop.[8] Kumada has, of course, reported some amino acid derived ligands which, for the reaction in equation (1), lead to e.e's of up to 83%.[7]



(2)

(**9**)

Yield 38%

$[\alpha]_D^{25} = -13.2°(c\,0.1, CHCl_3)$

Sulphides can serve as ligands in transition metal catalysed carbon–carbon bond forming reactions. Incorporation in chiral macrocycles offers a unique opportunity to transfer chirality *catalytically*. Extensions of this work with sterically rigid amino acid derived macrocyclic sulphides will be reported in due course.

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