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DESIGN OF LIGANDS DERIVED FROM SULFUR CONTAINING AMINO ACIDS FOR ENANTIOSELECTIVE CROSS COUPLING CATALYZED BY NICKEL. INTRAMOLECULAR PARTICIPATION OF SULFIDE

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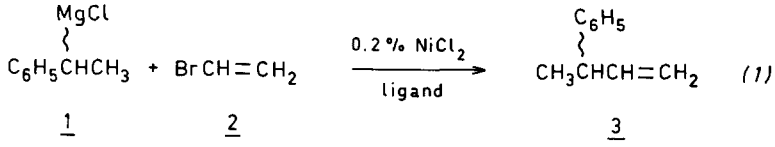
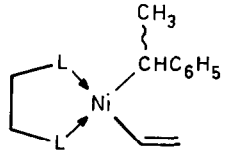
SUMMARY. A rationally designed ligand, 2-dimethylamino-1-diphenylphosphino-5-methylthiopentane (homomethphos) shows high efficiency in the nickel catalyzed cross coupling of the Grignard reagent from 1-chloro-1-phenylethane with vinyl bromide.

A key intermediate in the nickel catalyzed cross coupling of Grignard reagent (1) with vinyl bromide (2) to give 3-phenylbutene-1 (3) as shown in eq 1 is assumed to be the cis-diorganonickel (4), in the case that nickel bears a bidentate ligand.[1] Reductive



1 2 3 (1)

elimination, i.e. the crucial joining of the carbon-carbon bonds, in an analogue of postulated square planar 4 is known to be induced by tertiary phosphines.[2] The suggestion has been made,[2a] and is supported by calculations, that this catalyzed dissociation occurs



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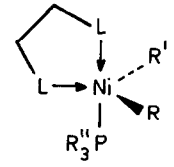

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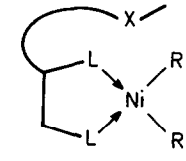
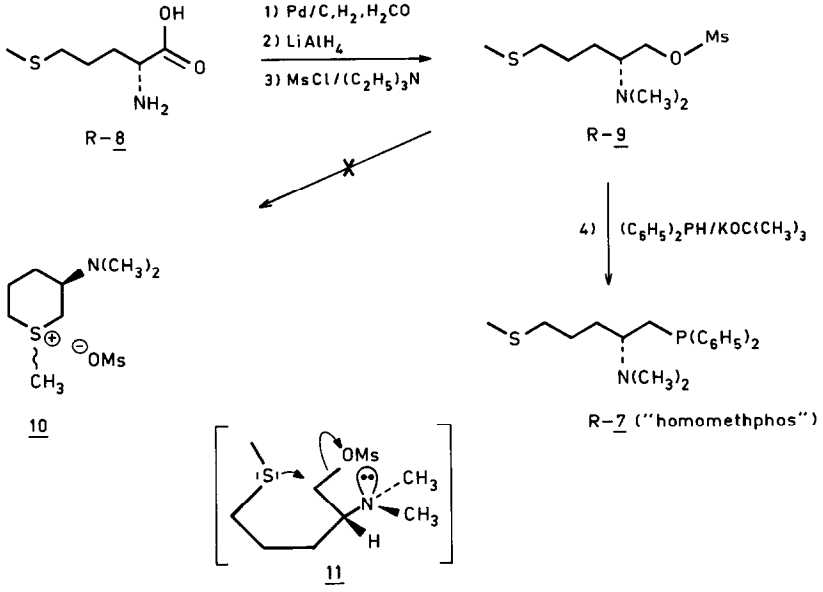


6

after a pseudorotation of 5, formed on axial attack of phosphine.[3,4] If this hypothesis is true, properly timed intramolecular attack by a correctly placed ligand should provide a means of guiding the reductive elimination; this thought is expressed in 6 where X is a suitable heteroatom.

Kumada, et. al.,[5] have shown that 2-dimethylamino-1-diphenylphosphino alkanes derived from amino acids are good ligands for the cross coupling shown in eq 1. We have reported that similar ligands obtained from (S-alkylated) cysteine and penicillamine, and from methionine are also suitable,[6] and that sulfide could fulfil the role of X in 6.[7] Detailed consideration of Corey-Pauling-Kolthun (CPK) models indicated, however, that the desired intramolecular participation of sulfur[8] is optimal only if it is separated from the chiral carbon by a chain of at least three carbon atoms. This could be realized in 7, derived from the amino acid, homomethionine (8), as illustrated for the (R) enantiomer.



R-8

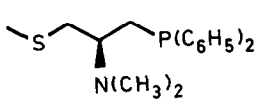
R-9

10

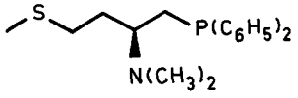
R-7 ("homomethphos")

11

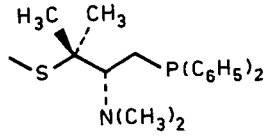
Prior to experiment we predicted that unwanted cyclization of 9 to 11 would be inhibited by the dimethylamino group.[9] Of the various conformations that could lead to cyclization, that illustrated (11) is probably best. An S_N2 process proceeding through this conformation requires that the mesylate be eliminated into the nucleophilic lone pair on nitrogen; other conformations present even greater problems. On the basis of these predictions homomethionine was synthesized and resolved on large scale, as described.[10] Ligand 7 was obtained in 47% overall yield. No cyclization was observed although this problem had completely frustrated earlier attempts we had made to obtain suitable materials for testing the hypothesis given in the previous paragraphs.



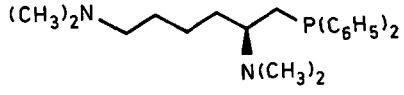
S-12



S-13



R-14



S-15

The results for the formation of 3 in the presence of previously described[6] (S)-"methylcysphos" (12), (S)-"methphos" (13), (R)"penphos" (14), and new (S)-"lysphos" (15), prepared from lysine, and (R)-7 are shown in the Table.

Table

Results for Ni Catalyzed Cross Coupling of 1 with 2.[a]

	enantiomeric excess (config) 3	
ligand	$NiCl_2$[b]	$NiCl_2$[c]
S-12 (methylcysphos)[d]	38(S)	e
S-13 (methphos)[d]	65(S)	59(S)
R-14 (penphos)[d]	42(R)	e
S-15 (lysphos)	58(S)	34(S)
R-7 (homomethphos)	70(R)	88(R)

a) ratio ligand/$NiCl_2$/1/2 is 1/1/250/125 in $(C_2H_5)_2O$; b) reaction at -50°C for 4 h followed by 16 h at 0°; c) reaction at -5°for 16 h; d) data taken from ref. 6; e)experiment not performed.

The enantiomeric excess of 3 obtained with (R)-7 is, to our knowledge, the best ever experimentally obtained for this coupling reaction.[11] The rotations of the coupling product were determined on neat, pure 3, isolated by preparative glc.

Were sulfur not coordinated at some stage in the enantioselectivity determining stages of the reaction at hand, the length and conformational mobility of the chain would preclude the selectivity observed here. We submit that the results obtained with 7 are in accord with the hypothesis advanced in the introductory paragraphs. The other sulfur containing ligands have side chains that are likely too short to allow effective participation of sulfur. The nitrogen atom of (S)-15 is probably too poor a ligand to coordinate and may also be complexed to Grignard reagent. The question of generality of this effect of sulfide in 7 is under investigation.[12]

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8. Ligation of $PdCl_2$ (the nickel complexes have not been obtained crystalline) occurs via phosphine and dimethylamine in S-13 and R-7 as established by an X-ray structural determination to be published.
9. Capon, B.; McManus, S.A.; "Neighboring Group Participation", Plenum Press, New York, 1976; Vol. 1.
10. Vriesema, B.K.; Kellogg, R.M.; Ten Hoeve, W.; Wynberg, H.; Boesten, W.H.J.; Meijer, E.M.; Schoemaker, H.E.; Tetrahedron Lett., preceding article.
11. An e.e. of 94% has been calculated in ref. 5a for 3 using a ligand derived from tert-butylglycine, which was not enantiomerically pure.
12. Acceptable analytical data and spectra consistent with the proposed structures were obtained for all new compounds.

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