Tetrahedron Letters,Vol.26,No.29,pp 3499-3502,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

MACROCYCLES WITH SULFIDE AND AMINE BINDING SITES AS CHIRAL LIGANDS FOR NICKEL CATALYZED CROSS COUPLING OF A GRIGNARD REAGENT WITH VINYL BROMIDE

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Summary: Synthetic routes to macrocycles derived from (S)-phenyl alanine and (S)-cysteine have been developed. The catalyzed coupling of the Grignard reagent of 1-chloro-1-phenylethane and vinyl bromide in the presence of these ligands proceeds usually in good yields and in enantiomeric excesses (e.e.) of up to 46%.

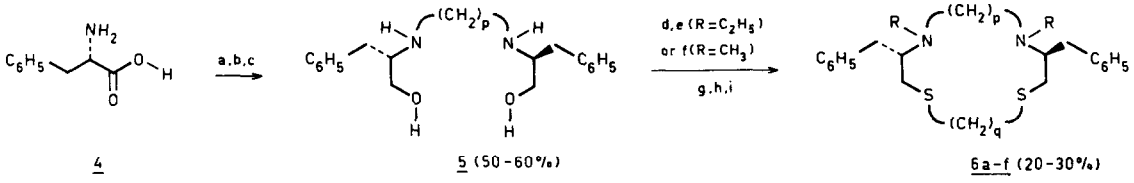
Sulfides,[1] besides the commonly used phosphines, can also act as ligands in the nickel catalyzed cross couplings illustrated in eq. 1.[2] Moreover, sulfide and amine sites may be combined in the same ligand in analogy with many recently investigated phosphine/amine-containing systems.[3,4] This combination of "hard" amine and "soft" sulfide is attractive for reactions like those of eq. 1 wherein mixed metal systems ("hard" magnesium and "softer" nickel) are involved.[5] The stereochemistry of the complexes can be manipulated by incorporation of these ligand sites in a macrocycle, the conformational restraints of which can guide the stereochemistry of bonding. The macrocyclic ligand complex serves then as a reasonably rigid template on which the coupling reaction occurs.

$$\underset{\underline{1}}{RCHCH_3(MgCl)} + \underset{\underline{2}}{BrCH{=}CH_2} \xrightarrow[\text{ligand}]{Ni^{2\oplus},(cat)} \underset{\underline{3}}{RCHCH{=}CH_2(CH_3)} + MgBrCl \qquad (1)$$

Our explorations with modifications of macrocyclic sulfides made chiral by the incorporation of a single tartaric acid[1] unit were not promising with regard to catalytic asymmetric induction in the products (3). To attain increased rigidity and better defined steric barriers a ligand series was designed in which amino acids, (S)-phenyl alanine in the present case, serve as the stereogenic elements. Both sulfide and amine sites are incorporated in the macrocycle, which has C_2 symmetry (equivalent faces). The ring-closure was accomplished via a cesium thiolate as shown in Scheme 1.[7] Such cesium mediated anionic S_N2 ring-closures are particularly efficacious for resolution of this type of synthetic problem.[8] The ethylation or methylation of nitrogen prior to ring-closure proceeded in 80-90%

yield. The yields of the cyclizations are lower than usual owing probably to the use of less reactive chloride as leaving group; the overall synthetic strategy was better compatible with this approach, however.[9]

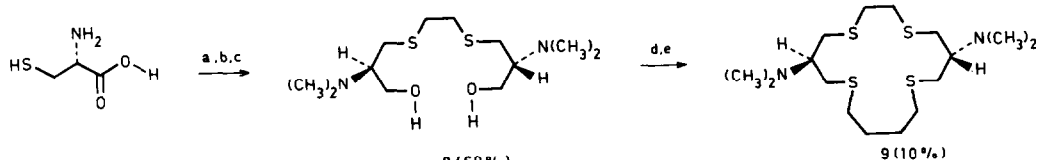
Scheme 1



4 5 (50-60%) 6a-f (20-30%)

a) $SOCl_2/CH_3OH$; b) $ClCO(CH_2)_{p-2}COCl/(C_2H_5)_3N/CH_2Cl_2$; c) $LiAlH_4/THF$; d) ($R=C_2H_5$) $CH_3COCl/(C_2H_5)_3N/CH_2Cl_2$; e) ($R=C_2H_5$) $LiAlH_4/THF$; f) ($R=CH_3$) H_2CO/HCO_2H; g) ($R=C_2H_5$ or CH_3) HCl/C_2H_5OH; h) $SOCl_2/CHCl_3$; i) $HS(CH_2)_qSH/Cs_2CO_3/DMF$.

Scheme 2



7 8 (60%) 9 (10%)

a) $NaHCO_3/BrCH_2CH_2Br$; b) $Pd/H_2/H_2CO$; c) $LiAlH_4/THF$; d) $SOCl_2/CHCl_3$; e) $HS(CH_2)_4SH/Cs_2CO_3/DMF$.

The results with 6a-f in the cross coupling reaction of eq 1 ($R = C_6H_5$) are given in Table 1. Reactions were run at -10^o to 0^o for 17 hr in ether under N_2 at 1:2:Ni(II):ligand (6) ratios of either 1:1:0.005:0.005 (condition 1) or 2:1:0.005:0.005 (condition 2). Yields of the coupling reaction are good and establish that, despite the considerable structural variation among the ligands, the sulfide/amine combination allows effective solubilization of the metal with no hint of poisoning. The rate of the ligand-free Ni-catalyzed coupling is not more than a tenth of the rate of the reactions described here.[1] The ligand-free reaction under these conditions can make at maximum a 10% contribution to the obtained yield.

The chemical yields are all good, and the enantiomeric excesses, although low, progress from no (6a,c) through 6b to 6d to 6e to modest e.e.'s. The use of excess Grignard reagent, condition 2, is known to lead to better e.e.'s.[4] In terms of structure 1,6-nitrogen and 1,5-sulfur bridge arrangements are superior. Methyl, rather than ethyl, is the better amine substituent. These results, although encouraging, indicate that further refinement of design is still necessary,

The catalytically active species in the reaction of eq 1 should be Ni(0).[10] This will be square planar.[11] With the aid of CPK models ligand 9 was developed (Scheme 2) in which Ni(0) can rest in a nearly optimal cavity bounded by four sulfides.[12] The nitrogen sites lie

Table. Cross Coupling of A and B in the Presence of Macrocycle.

Compound	R	P	Q		chemical yield 3[a]	e.e.(%)(abs. config.)[b]
6a	CH_2CH_3	2	2	1	80	0
6b	CH_2CH_3	3	3	1	88	4.5% (R)
6c	CH_2CH_3	2	4	1	83	0
6d	CH_2CH_3	4	3	1	88	4.5% (R)
6e	CH_3	4	3	1	90	9.5% (R)
	-	-	-	2	90	15% (R)
6f	CH_3	$-(CH_2)_2O(CH_2)_2$	$(CH_2)_2S(CH_2)_2S(CH_2)_2$	2	90	8.5% (R)
9	-	-	-	1	50	46 (R)
				2	95	25 (R)

a) Determined from ^{1}H NMR spectra as previously described.[4] b) Determined in duplicate, error range 1.5%.

outside the ring, and are derived from (S)-cysteine. Difficulties were encountered in the synthesis owing chiefly to the proclivity to rearrangement of the chloride derived from 8. The highest rotation measured for 9 is $[\alpha]_D^{21}$ - 89° (c 1, $CHCl_3$). The yield of coupling product (3) is lower than usual (Table). The enantiomeric excess in this catalytic process does reflect, however, clearly indeed the improved design of the ligand.

The routes to macrocyclic sulfide/amine ligands described here are flexible and allow much structural variation. A strategy for further exploration has been defined. Although a distressing number of mechanistic questions remain unresolved, and the e.e.'s for the test reaction used here are still lower than some other reports,[2a,b,4] the cardinal point has been established that rational ligand design is possible on the basis of even the existing (limited) mechanistic information. Further work is in progress following very recently postulated mechanistic lines.[11c]

Acknowledgement. We are grateful to N.A.T.O. for providing a fellowship for M.L. and for partial support of B.K.V. by the Netherlands Organization for the Advancement of Pure Research (Z.W.O.) administered through the Netherlands Foundation for Chemical Research (S.O.N.).

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(Received in UK 9 May 1985)