Chiral (Macrocyclic) Sulfide- and Sulfide/Alkylamino-Containing Ligands for Nickel-Catalyzed Grignard Cross-Coupling Reactions

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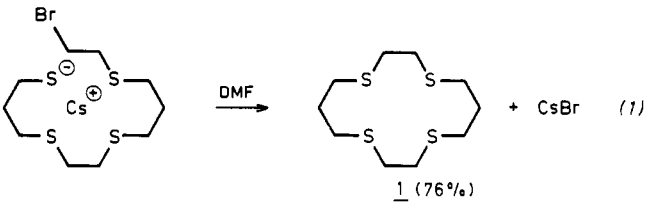
Some macrocycles that contain sulfide and/or amino linkages as coordination sites have been examined as ligands for the nickel-catalyzed cross-coupling of the Grignard reagent of 1-phenyl-1-chloroethane with vinyl bromide to provide (1-methyl-2-propenyl)benzene. The achiral macrocyclic sulfide 1,4,8,11-tetrathiatetradecane (1) was shown to be as good a ligand as triphenylphosphine for this reaction; the yields with either ligand were nearly quantitative. To prepare chiral macrocyclic ligands several routes were explored. First, (*R,R*)-diethyl tartrate was converted to its cyclohexanone acetal and then reduced to the diol. Mesylation followed by treatment with the dicesium salt of 3-thiapentane-1,5-dithiol afforded the desired macrocycle **17a** in 80% yield. In this manner other chains were also introduced. In another approach L-phenylalanine was coupled with the acid chloride of 1,ω-dicarboxylic acids. Reduction with $LiAlH_4$ removed the amide functionality and reduced the carboxylic esters to the hydroxymethylene stage. The secondary amine functionalities were methylated (formic acid/formaldehyde) or ethylated (acetyl chloride followed by $LiAlH_4$). Chlorination of the hydroxyl groups with $SOCl_2$ followed by ring closure with the dicesium salts of appropriate 1,ω-dithiols provided the desired macrocycles **21a–f**. The macrocycles **17** and **21** were examined, together with various model compounds, as ligands for the cross-coupling reaction. In most cases excellent yields of (1-methyl-2-propenyl)benzene were obtained but in very modest enantiomeric excess (maximally 17%). On the basis of these results a ligand, (6*R*,15*R*)-6,15-bis(dimethylamino)-1,4,8,13-tetrathiahexadecane (**24**), was prepared from L-cysteine. This ligand was developed to provide suitable square-planar coordination for the presumed nickel(0) and diorganonickel intermediates in the cross-coupling. In a catalytic reaction with a turnover of about 200, the product (1-methyl-2-propenyl)benzene was formed in an enantiomeric excess of 46%. An open-chain analogue of **24** provided only an 8% enantiomeric excess. Some general comments are made about macrocyclic ligands and about the symmetry properties of the complexes involved in the cross-coupling reaction.

Synthetic macrocycles have been used inventively for complexation of metal and organic cations, various anions, and neutral molecules.[1] Applications in, for example, selective extractions,[2] solubilization of salts,[3] redox reactions,[4] photoresponsive crown ethers,[5] and (membrane) transport systems,[6] as bridging components in cyclophanes and porphyrins,[7,8] and as enzyme mimicks[9] have been made.

Of great value for synthetic purposes are catalytic carbon–carbon bond-forming processes, several of which have been developed in recent years to a considerable degree of sophistication.[10,11] A (chiral) macrocycle, or family thereof, might be designed, making use of the opportunities for preorganization embodied in the macrocyclic framework, to ligate the catalytically active metal in a predictable fashion. Catalytic synthesis could be carried out on this metal/ligand framework. If the complex is chiral, a route to catalytic asymmetric synthesis is opened.[12] We are not aware of previous activity in this potentially fruitful area. The problems of design are appreciable, however. A major handicap is that the mechanisms of many of the interesting transition-metal-catalyzed processes are inadequately understood. Ligand design must draw therefore all too often on informed guesswork and intuition at the expense of logically constructed principles of design.

We saw an entry into this area via our previous experience in macrocyclic synthesis. Based on the use of *cesium salts*, a method for the synthesis of macrocyclic sulfides has been developed. The prototype reaction is illustrated in eq 1.[13] Synthesis of chiral variants of **1** and related macrocycles appeared a goal well within reach.[14] Could such materials display the desired template characteristics?

For the purposes of exploration, the nickel-catalyzed coupling of the (racemic) Grignard reagent **2** with vinyl bromide **3** to afford (1-methyl-2-propenyl)benzene (**4**) was examined (eq 2).[15] The postulated mechanism for this reaction will be discussed subsequently. This reaction is



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(1) Brief topical reviews: (a) Lehn, J.-W. *Science (Washington, D.C.)* **1985**, *227*, 849. (b) Hayward, R. C. *Chem. Soc. Rev.* **1983**, *12*, 285.

(2) Saito, K.; Masuda, Y.; Sekido, E. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 189.

(3) Takagi, M.; Ueno, K. *Host Guest Complex Chemistry. Macrocycles, Synthesis, Structures, Applications*; Vögtle, F., Weber, E., Eds.; Springer Verlag: Berlin, 1985; pp 217–243.

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Table I. Influence of Various Ligands on the Formation of 4

ligand	method[a]	yield 4,[b] %
none	A	10
$(C_6H_5)_3P$	B	95
$(n\text{-}C_4H_9)_2S$	B	50
$[CH_3S(CH_2)_2SCH_2]_2CH_2$	B	50
1	B	95

[a] Reaction conditions: method A, Grignard reagent/vinyl bromide (0.8); method B, Grignard reagent/vinyl bromide (2), $NiCl_2$ (ligand)/vinyl bromide (10^{-2}); Solvent diethyl ether; reaction time 18 h at −10 °C. [b] Determined by ^1H NMR analysis of crude reaction mixtures.

useful for test purposes because it has been well studied and the optical rotation of product **4** is appreciable and known for pure material; $[\alpha]^{20}_D$ −5.91° (1 dm, neat).[15d]

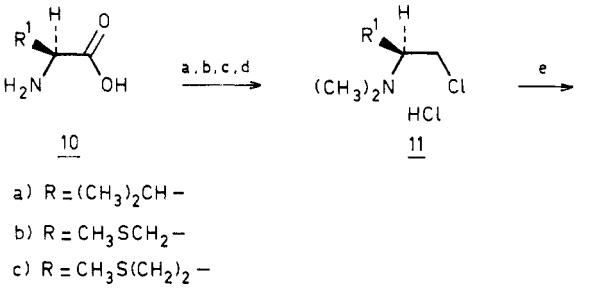
A question arises immediately with regard to the projected approach. For the reaction of eq 2, the $NiCl_2$ present in catalytic amounts must be solubilized with an organic ligand. Triphenylphosphine or 1,3-diphosphinopropane succeeds admirably for this purpose.[15] Extensive work on the catalytic enantioselective synthesis of **4** has been done using chiral phosphine- or phosphine/dialkylamino-containing ligands (see further). But could a sulfide be used instead of a phosphine? Sulfides are generally considered to be poorer ligands than phosphines[16] and have also the reputation of being poisons for transition metals.[17]

With this background and these questions in mind we turned to the synthesis and investigation of a variety of ligands.[18]

Results and Discussion

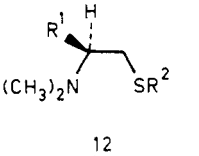
A. Sulfides as Ligands. The catalytic synthesis of **4** was carried out under otherwise identical conditions with no ligand and triphenylphosphine, di-*n*-butyl sulfide, **1**, and 2,5,9,12-tetrathiatridecane (**25**) (an open-chain analogue of **1**) as ligands. The results of this brief survey are summarized in Table I. We were pleased to observe that the coupling proceeds well indeed in the presence of **1**.

Scheme I[a]



10 11

a) $R = (CH_3)_2CH-$
b) $R = CH_3SCH_2-$
c) $R = CH_3S(CH_2)_2-$



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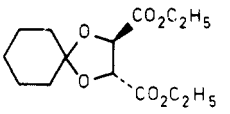
	R^1	R^2
a)	$(CH_3)_2CH-$	C_2H_5-
b)	$(CH_3)_2CH-$	C_6H_5-
c)	CH_3SCH_2-	C_2H_5-
d)	CH_3SCH_2-	$C_6H_5CH_2-$
e)	$CH_3S(CH_2)_2-$	C_2H_5-
f)	$CH_3S(CH_2)_2-$	C_6H_5-

[a] Reagents: (a) H_2CO, Pd/C; (b) $LiAlH_4$; (c) HCl; (d) $SOCl_2$; (e) R^2SNa.

This stands in contrast to di-*n*-butyl sulfide, which clearly is a poor ligand. The nonmacrocyclic ligand, 2,5,9,12-tetrathiatridecane, at least on the basis of these qualitative experiments, is also less effective than **1**. Very likely the conformational preorganization of **1** relative to its open-chain analogue contributes to the effectiveness of **1**. Particularly encouraging is the fact that sulfides fortunately have no observable tendency to poison the catalyst. Encouraged by these results, we turned to chiral systems.

B. Synthesis. In the initial investigations considerable use was made of the cyclohexanone acetal of D-diethyl tartrate **5**. By uneventful procedures the open-chain



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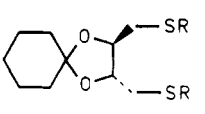
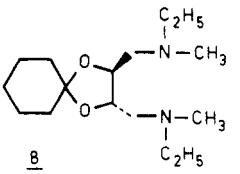


6 R = C_2H_5
7 R = C_6H_5



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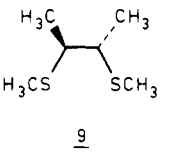

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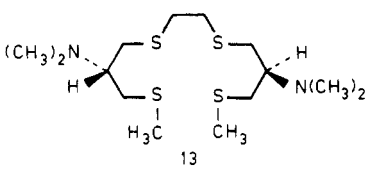

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compounds **6**–**8** were obtained. (*S*,*S*)-**9** was obtained by alkylation of the corresponding known dithiol.[19] The

(10) (a) Bosnich, B.; Fryzuk, M. D. In *Topics in Inorganic and Organometallic Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, 1981; Vol. 12, pp 119–154.

(11) Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1980.

(12) This point is important with regard to enzyme models. In many cases the compound designed and synthesized as model is used on a stoichiometric basis. This is inefficient both in terms of design as well as in practical application; very often a compound of quite high molecular weight must be used with a lower molecular weight substrate. Not only is this wasteful but it leads to experimental problems in following the reaction and in isolation of the product(s).

(13) (a) Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4481. (b) Buter, J.; Kellogg, R. M. *Org. Synth.*, in press.

(14) For a similar approach wherein carbon–nitrogen bonds are formed in the macrocyclization step, see: Vriesema, B. K.; Buter, J.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 110.

(15) (a) Consiglio, G.; Botteghi, C. *Helv. Chim. Acta* **1973**, *56*, 460. (b) Consiglio, G.; Morandini, F.; Picolo, O. *Tetrahedron* **1983**, *39*, 2699. (c) Consiglio, G.; Morandini, T.; Picolo, O. *J. Chem. Soc., Chem. Commun.* **1983**, 112. (d) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagobani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180. (e) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195. Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic: New York, 1975; Vol. II, pp 246–295.

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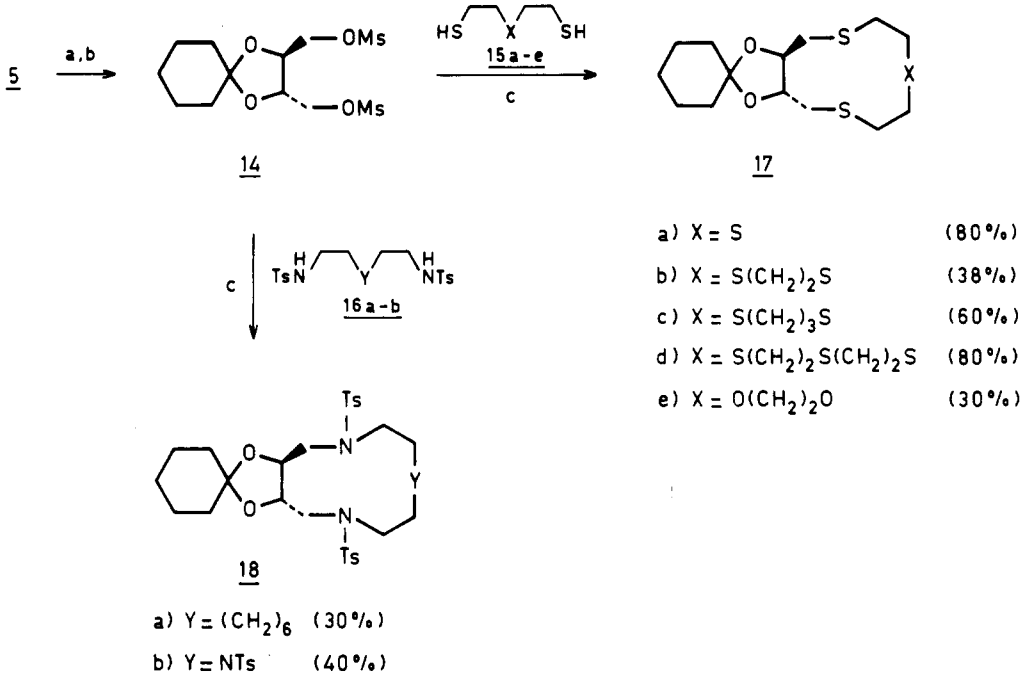
(17) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin: Reading, MA, 1972; pp 1–44.

(18) Two preliminary communications on the present work have appeared: (a) Lemaire, M.; Buter, J.; Vriesema, B. K.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1984**, 309. (b) Lemaire, M.; Vriesema, B. K.; Kellogg, R. M. *Tetrahedron Lett.* **1985**, 3499.

(19) Corey, E. J.; Mitra, R. B. *J. Am. Chem. Soc.* **1962**, *84*, 2946.

Scheme II[a]



[a] Reagents: (a) $LiAlH_4$; (b) MsCl/pyridine; (c) Cs_2CO_3/DMF.

open-chain ligands **12a–f** were prepared by adaption of literature procedures from L-valine, L-cysteine, and L-methionine as shown in Scheme I. L-*S*-Methylcysteine (**10b**) was synthesized following the literature route.[20] In addition, podand **13** was made by coupling of **11b** with ethanedithiol.[21]

The intermediates **5** were examined as chiral units for incorporation into chiral macrocycles. Various syntheses of achiral thia crown ethers have been described,[1,9b,13,22,23] but chiral examples are scarce.[24] Transformation of **5** to the mesylate **14** allowed the ready preparation of **17a-e** and **18a,b** making use of the cesium salt approach to macrocycle synthesis (Scheme II). The yields refer to pure product isolated from the cyclization step. The procedures for macrocyclization follow already described precedent.[13] The cyclized materials were in general fairly tractable and could be purified without excessive difficulty.

A different strategy to chiral macrocycles involves the incorporation of two identical chiral units to provide steric barriers on both sides of the macrocyclic framework. Amino acids lend themselves well to this purpose. L-Phenylalanine was chosen for use. The simple strategy followed is detailed in Scheme III. Coupling of L-phenylalanine with acid chlorides of dicarboxylic acids proceeded uneventfully. Amines **20** were either ethylated (CH_3COCl followed by $LiAlH_4$) or methylated (H_2CO/HCO_2H). Activation of the hydroxyl group followed by cyclization with the cesium salt of the requisite dithiolate provided **21a–f**. The yields of these materials are only moderate (16–26%), owing chiefly to difficulties in purification of these quite polar macrocycles.

All the macrocycles were characterized by spectral and analytical means. We assume unless otherwise stated that all of the ligands prepared are enantiomerically pure.

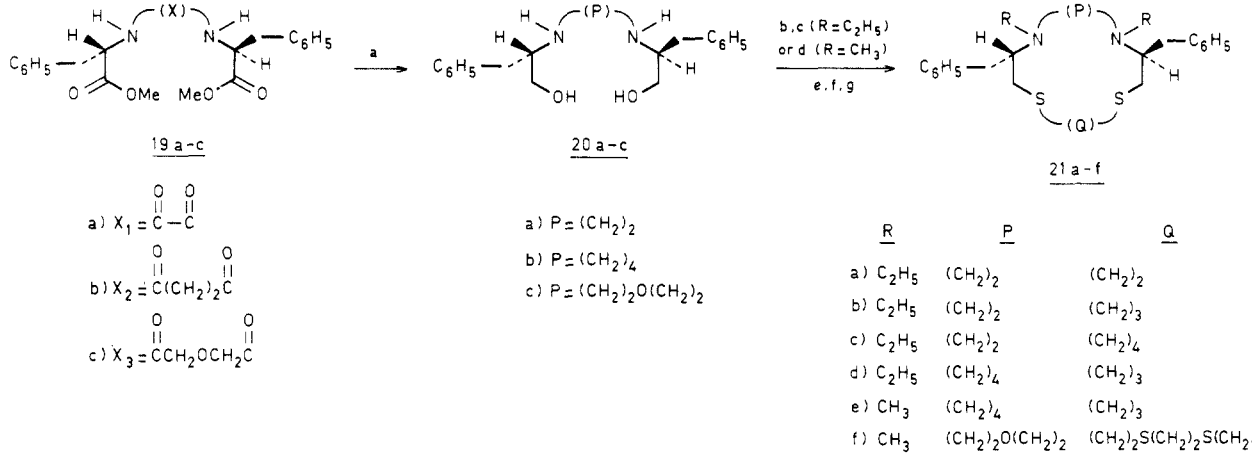
Another variation of the macrocyclic theme is **24** in which the four sulfur units of podand **13** are contained in a 16-membered ring (Scheme IV). The rationale behind the design is discussed in the following section. A synthetic route considerably different from that leading to readily obtainable **13** (unfortunately) had to be followed. Coupling of L-cysteine with 1,2-dibromoethane followed by exhaustive methylation with formaldehyde under catalytic reductive conditions and reduction with $LiAlH_4$ in THF gave **23**. The classical Eschweiler–Clarke approach was unsatisfactory in this case. The macrocyclization was accompanied by severe difficulties as a result of the lability of **23b**. Mixtures of products, including what is likely a meso epimer of **24**, were isolated (see the Experimental Section). Apparently, in this case **23b** undergoes cyclization to thiatanium ion **25** (Scheme V), which can be reopened with epimerization. This process can best be circumvented by employment of low temperatures and rapid workup procedures.

C. Cross-Coupling Reactions. The generally postulated mechanism for the cross-coupling reaction studied here is shown in Scheme VI for the coupling of vinyl bromide to a Grignard reagent.[11] Formation of a nickel(0) complex (**26**) is thought to initiate the reaction. On the basis of the work of Kochi[25] and Yamamoto[26] the presumed intermediate **28**, from which reductive elimination takes place, is predicted to have a square-planar arrangement of ligands.

Assuming the correctness of the square-planar postulate, three general stereochemical possibilities are worth con-

(20) Theodoropoulou, D. *Acta Chem. Scand.* **1959**, *13*, 383.
(21) For a discussion of podands, see: Vögtle, F.; Weber, E. *Angew. Chem.* **1979**, *91*, 813.
(22) (a) Voronkov, M. G.; Knatov, V. I. *Russ. Chem. Rev.* **1982**, *51*, 856. (b) Klieser, B.; Rossa, L.; Vögtle, F. *Kontakte* **1984**, *1*, 3. (c) Schroth, W.; Poleschner, H.; Gubler, M.; List, A. *Z. Chem.* **1985**, *25*, 138. (d) Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *Tetrahedron Lett.* **1983**, *24*, 3243. (e) Newkome, G. R.; Taylor, H. C. R.; Fronczek, F. R.; Delord, T. J. *J. Org. Chem.* **1984**, *49*, 2961.
(23) See also, for example: (a) Dietrich, B.; Hosseini, M. W.; Lehn, J.-M.; Sessions, R. B. *Helv. Chim. Acta* **1985**, *68*, 289. (b) Vögtle, F.; Kissener, W. *Chem. Ber.* **1984**, *117*, 2538. (c) Weber, E.; Josel, H. P.; Puff, H.; Franken, S. *J. Org. Chem.* **1985**, *50*, 3125.
(24) (a) Picard, C.; Cazaux, L.; Tisnes, P. *Tetrahedron Lett.* **1984**, *25*, 3809. (b) Sasaki, S.; Koga, K. *Heterocycles* **1979**, *12*, 1305.
(25) (a) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547. (b) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319.
(26) (a) Komiya, S.; Abe, Y.; Yamamoto, A.; Yamamoto, T. *Organometallics* **1983**, *2*, 1466. (b) Tatsumi, K.; Nakamura, A.; Komiya, S.; Yamamoto, A.; Yamamoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 8181.

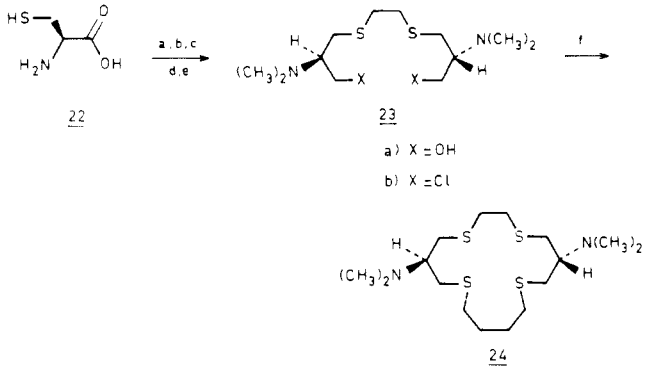
Scheme III[a]



	R	P	Q
a)	C_2H_5	$(CH_2)_2$	$(CH_2)_2$
b)	C_2H_5	$(CH_2)_2$	$(CH_2)_3$
c)	C_2H_5	$(CH_2)_2$	$(CH_2)_4$
d)	C_2H_5	$(CH_2)_4$	$(CH_2)_3$
e)	CH_3	$(CH_2)_4$	$(CH_2)_3$
f)	CH_3	$(CH_2)_2O(CH_2)_2$	$(CH_2)_2S(CH_2)_2S(CH_2)_2$

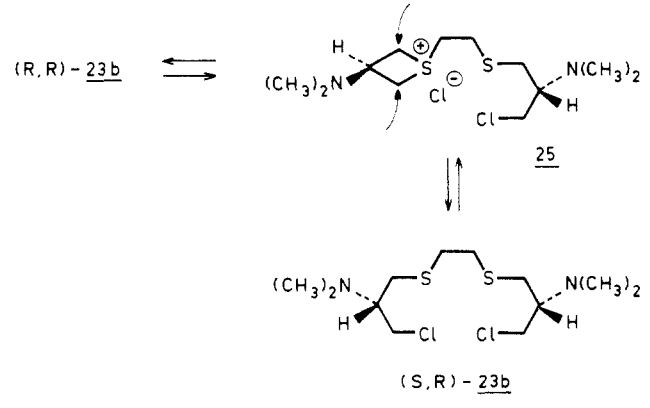
[a] Reagents: (a) $LiAlH_4$/THF; (b) (R = C_2H_5) $CH_3COCl/(C_2H_5)_3N/CH_2Cl_2$; (c) (R = C_2H_5) $LiAlH_4$/THF; (d) (R = CH_3) H_2CO/HCO_2H; (e) (R = C_2H_5, CH_3) HCl/C_2H_5OH; (f) $SOCl_2/CHCl_3$; (g) $HS(Q)SH/Cs_2CO_3$/DMF.

Scheme IV[a]

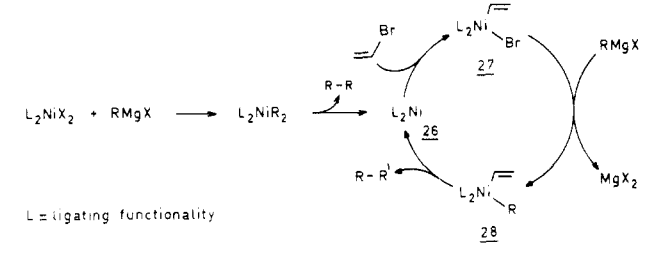


[a] Reagents: (a) $NaHCO_3/Br(CH_2)_2Br$; (b) $Pd/C/H_2/H_2CO$; (c) $LiAlH_4$/THF; (d) HCl/C_2H_5OH; (e) $SOCl_2/CHCl_3$; (f) $HS(CH_2)_4SH/Cs_2CO_3$/DMF.

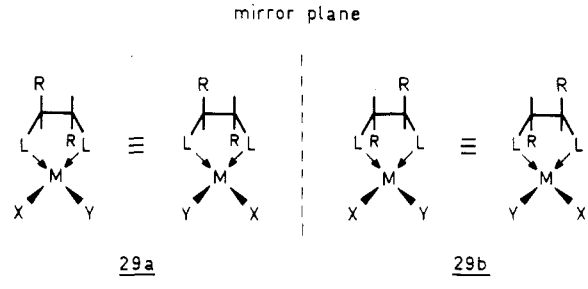
Scheme V



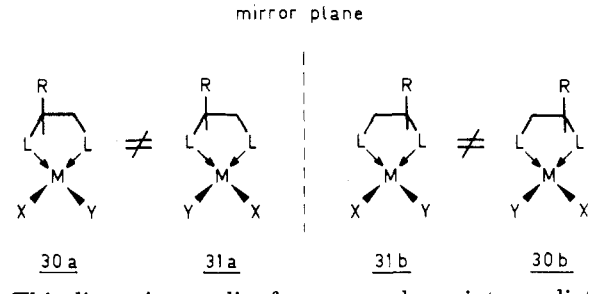
Scheme VI



sidering for **27** and **28** where L_2 represents a cis-fused bidentate ligand. If the bidentate ligand is achiral, there is a single stereoisomer of either **27** or **28**. However, if the bidentate ligand is chiral and has a C_2 axis, then there are two enantiomeric possibilities differing in the relative configurations at the chiral center in the ligand, as illustrated with general formula **29**. The metal center is not



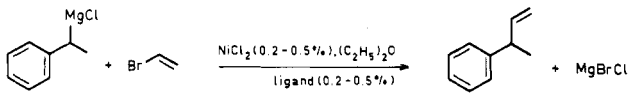
stereogenic but is chirotopic.[27] If the bidentate ligand is chiral as the result of incorporation of a single asymmetric carbon atom and lacks a C_2 axis, the metal center becomes stereogenic, and two diastereomers for each enantiomer of the *ligand* are possible as illustrated with **30** and **31** (**a** and **b** are enantiomers). In other words, only in the latter case is the metal atom a center of diastereoisomerism.



This discussion applies for square-planar intermediates, and the stereochemical considerations above are based on the simplest form of argument wherein a single bidentate ligand is attached to the metal. In practice the complexity of the macrocyclic ligands is such that a decision between different modes of ligation is sometimes difficult. In the examples discussed here the macrocyclic ligands (but *not* their dialkylnickel complexes, see further) fulfill the case of C_2 symmetry whereas some of the alicyclic ligands lack a C_2 symmetry axis. It deserves emphasis that for the reactions at hand the presence of a C_2 symmetry axis could

(27) Following the use as defined by: Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

Table II. Asymmetric Nickel-Catalyzed Cross-Coupling of Grignard Reagent with Vinyl Bromide



2 3 4

entry	ligand	method[a]	ee, % [confign][b]	yield,[c] %
1		d		53
2	**6**	A		53
3	**6**	B		80
4	**7**	A		50
5	**8**	A		45
6	**9**	A	0.8 [*R*]	90
7	**12a**	A		81
8	**12b**	A		90
9	**12c**	A	1 [*R*]	90
10	**12d**	A	4.3 [*R*]	90
11	**12e**	A	3.5 ([*S*]	87
12	**12f**	A	1 [*R*]	89
13	**13**	A	7.7 [*S*]	88
14	**32**	A[e]	7 [*R*]	74
15	**32**	f	14 [*R*]	81
16	**33**	B	59 [*S*]	>90[23]

[a] Method A: Ratio 2:3 is 0.8. Method B: ratio 2:3 is 2. [b] For enantiomerically pure (*R*)-3-phenylbut-1-ene a value of $[\alpha]^{20}_D$ −5.91° (1 dm, neat) was used.[15d] [c] Yields of 3-phenylbut-1-ene determined from ^{1}H NMR spectra of crude product mixtures. [d] After 48 h instead of the normal conditions (one night). [e] See ref 15a. [f] See ref 29.

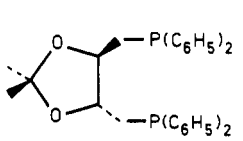
Table III

entry	ligand	method[a]	ee, % [confign][b]	yield,[c] %
1	**17a**	B	2.7 [*S*]	95
2	**17b**	A	9.7 [*S*]	87
3	**17b**	B	16.9 [*S*]	100
4	**17c**	B	2.0 [*S*]	95
5	**17d**	B	3.8 [*S*]	95
6	**17e**	B		77
7	**18a**	A		77
8	**18b**	A		74
9	**21a**	A		80
10	**21b**	A	4.5 [*R*]	88
11	**21c**	A		83
12	**21d**	A	4.5 [*R*]	88
13	**21e**	A	9.5 [*R*]	90
14	**21e**	B	15.0 [*R*]	90
15	**21f**	B	8.5 [*R*]	90
16	**24**	A	46 [*R*]	50
17	**24**	B	25 [*R*]	95

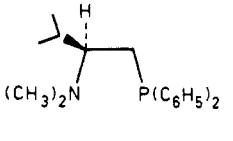
[a–c] See Table I.

be deleterious for the reason discussed above. Indeed, very remarkable results have been obtained in stereochemically complex cases wherein chiral ligands devoid of a C_2 axis have been used.[15e,28]

The results of the coupling reactions for alicyclic ligands are collected in Table II and those for macrocyclic ligands in Table III. Consider first the results in Table II. The ligands **6**–**8** (entries 2–5) are barely active as ligands as anticipated also from the results of Table I. A moderate chemical yield of **4** (entry 3) can be obtained by using excess Grignard reagent, but there is no enantiomeric excess. A comparison with (+)-**32** (DIOP)[15a,29] is useful (entries 14 and 15); moderate chemical yields of **4** are obtained but with low enantiomeric excesses. A sharp improvement in chemical yield occurs on turning to the ligands **9**, **12**, and **13**. The ^{1}H NMR spectra of the reaction



32



33

mixtures for these examples are clean and reveal only the formation of **4**; the yield estimates are lower limits. Ligand **9** is chemically efficient but provides no significant ee. Ligands **12** also lead to good chemical yields but poor ee values. The presence or absence of a C_2 symmetry axis has no observable influence on the (very low) ee values for these examples. Note, however, that *phosphine* ligand **33** (entry 16) leads to enantiomeric excesses of 59–81%.[15e,28] The point seems clear; the substitution on a carbon framework in a 1,2 fashion of sulfide/sulfide (**9**), phosphine/amino (**33**), or sulfide/dialkylamino leads in general to good ligands as judged from the yield of **4**. The higher enantiomeric excesses of **4** achieved with phosphine ligands must be due in large part to the higher degree of substitution about phosphine (tridentate with a unique conformation of aryl rings)[30] compared to bidentate sulfide, rather than a profound difference in chelating ability.

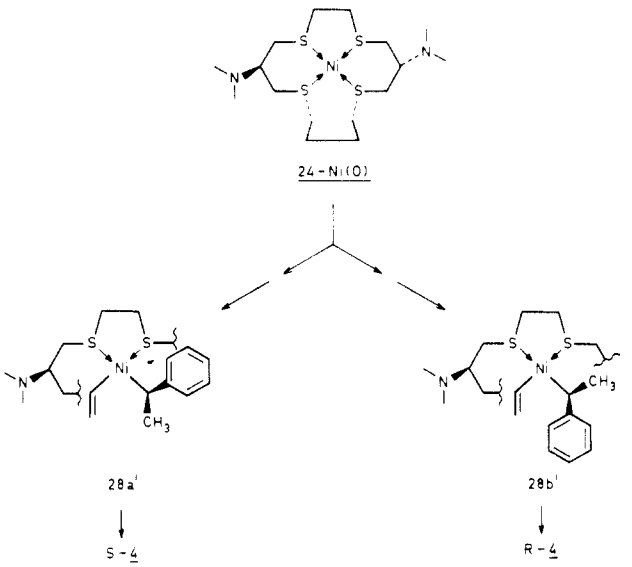
Can the problem of lesser substitution about sulfide as compared to phosphine be solved by some form of conformational control? A crude attempt to achieve this with podand **13** (entry 13) was not especially promising although the ligand leads to good chemical yields. The macrocyclic systems (Table III) offer better opportunities for achieving this objective. The macrocyclic sulfides **17** contain only a single chiral unit, i.e. the tartaric acid derived segment, which occupies a single side of the chain. These serve well as ligands, and the enantiomeric excess of **17b** rises promisingly when excess Grignard reagent is used (entries 2 and 3). This effect, which we have observed before,[28] probably stems from suppression of kinetic resolution of the Grignard reagent, which appears to racemize on about the same time scale as that of the coupling reaction.[31]

The series **21a–f**, in which two chiral segments on opposite sides of the macrocycle are incorporated, is disappointing in terms of enantiomeric excess of **4**. Again with **21e**, as with **17b**, the ee values increase mildly with increasing ratio of Grignard to vinyl bromide. It appears also that methyl rather than ethyl substitution at the nitrogen sites leads to marginally better results.

On the basis of these observations, we attempted to prepare a macrocycle that would provide square-planar coordination for both a nickel(0) intermediate (**26** in Scheme VI, but surrounded by four sulfide ligating sites) and presumed *cis*-diorganonickel(II) intermediate **28**. In the absence of suitable crystallographic data (none of the macrocycles prepared gave crystalline nickel or palladium complexes) recourse was taken in Corey–Pauling–Kolthun (CPK) models. These considerations led to **24**, the (difficult) synthesis of which has been described. Formally, **24** is the result of ring closure of podand **13** with a tetramethylene bridge. The presumed complex **24**–Ni(0) is illustrated in Scheme VII. Again on the basis of CPK models and the assumption of square-planar geometry in **28**, ultimate ligation of the vinyl and *sec*-alkyl groups is *postulated* to occur cis, with the two sulfide ligands still

(28) Griffin, J. H.; Kellogg, R. M. *J. Org. Chem.* **1985**, *50*, 3261 and references contained therein.
(29) Kiso, Y.; Yamao, K.; Miyake, N.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, 3.
(30) Brown, J. M.; Chaloner, P. A.; Parker, D. In *Catalytic Aspects of Metal Phosphine Complexes*; Aleya, E. C., Meek, D. W., Eds.; *Advances in Chemistry Series 196*; American Chemical Society: Washington, DC, 1982; p 337.
(31) Lindsell, W. E. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982, Vol. 1, pp 156–187.

Scheme VII



present arranged 1,4 with respect to each other. This mode of complexation presents the most space about nickel for the attachment of the organic groups. The *complex* still lacks a C_2 axis, and the Ni is therefore a stereogenic center. The set of diastereomers **28a'**/28b' (illustrated) is predicted to be more stable than the set with the organic groups interchanged (not illustrated) for obvious steric reasons. Complex **28b'** is predicted on steric grounds to be favored over **28a'**. If the coupling of the organic groups on nickel occurs with retention of configuration at carbon, then favored **28b'** should lead to (*R*)-**4**, in agreement with experiment (entries 16 and 17, Table III). The operation of a macrocyclic effect with the desired conformational control is clear; podand **13** leads to only an 8% ee of **4**, whereas a maximum ee of 46% can be obtained with **24**. These reactions involve a turnover of about 200 on each template molecule. We cannot rationalize readily the variation in ee with the conditions (entries 16 and 17).

We are painfully aware of the degree of speculation that has gone into the above arguments. However, despite the crudeness of the reasoning, the results are encouraging. Improvement is clearly necessary, and this can be achieved by a better understanding of the mechanisms of the coupling reaction, in particular the process whereby the organic fragments are joined on the nickel atom. Information on this point will be published separately and will be used as a basis for further work.[32]

Experimental Section

General Methods. Melting points were recorded on a Thermopan Reichert Austria apparatus. ^{1}H NMR spectra (Me_4Si internal standard) were recorded on a 60-MHz Varian, Jeol, or Perkin-Elmer instrument. ^{13}C NMR spectra were obtained at 25.16 MHz on a Varian XL-100 instrument. Mass spectral measurements were carried out on an AEI-MS9 instrument operating at 70 eV. Optical rotations wer measured with a Perkin-Elmer 241 polarimeter. Medium-pressure liquid chromatography was carried out on an instrument built in these laboratories;[33] a Waters apparatus was used for analytical work.

Compounds cited without reference either were in stock or were prepared by unexceptional literature procedures. The dithiols were all prepared by treatment of the corresponding dibromides with excess thiourea in alcohol followed by hydrolysis with base. Amino acid starting materials were purchased from Janssen Chimica. 1-Phenethyl chloride was prepared by treating (+)-1-phenethyl alcohol with $SOCl_2$ in $CHCl_3$. Microanalyses were done by the analytical division of these laboratories.

2,3-Bis[(ethylthio)methyl]-1,4-dioxaspiro[4,5]decane (6). To a stirred solution of 1.2 mmol of sodium ethoxide in 10 mL of ethanol under nitrogen atmosphere was added 1.2 mmol of ethanethiol and 0.5 mmol of the bis(mesylate) **14**.[14] The suspension was refluxed for 2 h. After evaporation of the solvent, the product was taken up in ether and washed with water. The ether was dried over $MgSO_4$. After filtration and evaporation the crude product was purified by chromatography over SiO_2 with ether as eluent: yield 1.0 mmol (85%); $[\alpha]^{20}_D$ −7.34° (*c* 1, $CHCl_3$); mass spectrum, parent *m/e* 290 (theory 290); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6 H), 1.57 (m, 10 H), 2.9 (q, 4 H), 2.95 (m, 4 H), 4.9 (m, 2 H).

2,3-Bis[(phenylthio)methyl]-1,4-dioxaspiro[4,5]decane (7). To a stirred solution of 15 mmol of sodium ethoxide in 30 mL of ethanol under nitrogen atmosphere was added 15 mmol of thiophenol and 5 mmol of the bis(mesylate) **14**. The suspension was refluxed for 3 h. After workup (see above) the crude product was purified by chromatography over SiO_2 with hexane/ethyl acetate (70:30) as eluent: yield 4.35 mmol (87%); $[\alpha]^{20}_D$ +15.7° (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.6 (m, 10 H), 3.2 (m, 4 H), 4.1 (m, 2 H), 7.2 (m, 10 H); mass spectrum, exact mass *m/e* 386.134 (theory 386.137).

2,3-Bis[(*N*-methyl-*N*-ethylamino)methyl]-1,4-dioxaspiro[4,5]decane (8). The diester **5** (10 mmol) was added to a solution of 30 mL of 30% methylamine in ethanol. After 1 h at room temperature the solvent was evaporated and the solid residue recrystallized from ether to give 90% of the diamide: ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 10 H), 2.9 (d, 6 H), 4.5 (s, 2 H), 7.05 (m, 2 H).

The diamide (8 mmol) was reduced with $LiAlH_4$ in diethyl ether to the corresponding amine: 3.2 mmol (40%); ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 10 H), 2.55 (s, 6 H), 2.65 (m, 4 H), 3.75 (m, 2 H).

The amine (3 mmol) was acetylated with acetyl chloride and triethylamine in ether. After 30 min at 20 °C, the ether layer was washed with water and dried over $MgSO_4$. After filtration and evaporation the crude product was purified by chromatography over SiO_2 with ethyl acetate as eluent to give the corresponding amide: 1.56 mmol (52%); ^{1}H NMR ($CDCl_3$) δ 1.6 (s, 10 H), 2.1 (s, 6 H), 3.0 (s, 6 H), 3.9 (m, 6 H).

Finally, this amide (1.5 mmol) was reduced with $LiAlH_4$ in THF under reflux for 5 h. After workup the crude ligand **8** was purified by chromatography over SiO_2 with chloroform as eluent: yield 0.6 mmol (40%); $[\alpha]^{20}_D$ −8.3° (*c* 2, CH_2Cl_2); mass spectrum, parent *m/e* 284 (theory 284); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 6 H), 1.6 (s, 10 H), 2.32 (s, 6 H), 2.6 (m, 8 H), 3.85 (m, 2 H).

(*R*,*R*)-2,3-Bis(methylthio)butane (9). To a stirred solution of 15 mmol of sodium ethoxide in 30 mL of ethanol was added 3 mmol of (*R*,*R*)-2,3-butanedithiol and 12 mmol of methyl iodide. After 24 h at room temperature the solvent was evaporated. The product was taken up in ether and washed with water. The ether was dried over $MgSO_4$. After filtration and evaporation and crude product was purified by chromatography over SiO_2 with ether as eluent, affording 1.53 mmol (51%) of **9**: $[\alpha]^{20}_D$ −36.6° (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 6 H), 2.1 (s, 6 H), 3.0 (m, 2 H).

General Procedure for Preparation of Ligands 12a–f and 13. The dimethylamino chlorides **11b,c** were prepared analogously to the method described for **11a**.[15e] The corresponding dimethylamino alcohols were previously described by us (**11b,c**)[28] and others (**11a**).[15e]

To a stirred solution containing 25 mmol of sodium ethoxide in 40 mL of C_2H_5OH was added 16 mmol of the thiol and 8 mmol of the chloride **11a–c**. The suspension was refluxed for 17 h. After evaporation the mixture was taken up in ether and washed with water. The ether layer was dried over $MgSO_4$. After filtration and evaporation the crude product was purified by chromatography over SiO_2 (see entries below for the separate compounds).

(*S*)-2-(Dimethylamino)-1-(ethylthio)-3-methylbutane (12a) was prepared from the chloride **11a** and ethanethiol. The product was purified by chromatography over SiO_2 with *n*-hexane/CH_2Cl_2 (70:30) as eluent: yield 3.04 mmol (38%); $[\alpha]^{20}_D$ +16.9° (*c* 1, CH_2Cl_2); mass spectrum, parent *m/e* 175 (theory 175); ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 6 H), 1.3 (t, 3 H), 1.9 (m, 1 H), 2.4 (s, 6 H), 2.65 (m, 5 H).

(32) Vriesema, B. K.; Kellogg, R. M. accepted for publication in *Tetrahedron Lett.*

(33) Clark Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(*S*)-2-(Dimethylamino)-1-(phenylthio)-3-methylbutane (12b) was prepared from the chloride **11a** and thiophenol. The product was purified by chromatography over SiO_2 with CH_2Cl_2 as eluent: yield 7.04 mmol (88%); $[\alpha]^{20}_D$ +37.6° (*c* 1, CH_2Cl_2); mass spectrum, parent *m/e* 223 (theory 223); ^1H NMR ($CDCl_3$) δ 1.05 (d, 6 H), 2.05 (m, 1 H), 2.4 (s, 6 H), 3.1 (m, 3 H), 7.3 (m, 5 H).

(*S*)-2-(Dimethylamino)-1-(ethylthio)-3-(methylthio)-propane (12c) was prepared from the chloride **11b** and ethanethiol. The product was purified by chromatography over SiO_2 with diethyl ether as eluent: yield 3.2 mmol (40%); $[\alpha]^{20}_D$ +1.42° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.3 (t, 3 H), 2.2 (s, 3 H), 2.4 (s, 6 H), 2.85 (m, 7 H); mass spectrum, exact mass *m/e* 193.095 (theory 193.096).

(*S*)-2-(Dimethylamino)-1-(benzylthio)-3-(methylthio)-propane (12d) was prepared from the chloride **11b** and benzyl mercaptan. The product was purified by chromatography over SiO_2 with diethyl ether as eluent: yield 5.68 mmol (71%); $[\alpha]^{20}_D$ −7.0° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 2.1 (s, 3 H), 2.2 (s, 6 H), 2.6 (m, 5 H), 3.76 (s, 2 H), 7.35 (s, 5 H); mass spectrum, exact mass *m/e* 255.112 (theory 255.112).

(*S*)-2-(Dimethylamino)-1-(ethylthio)-4-(methylthio)butane (12e) was prepared from the chloride **11c** and ethanethiol. The product was purified by chromatography over SiO_2 with CH_2Cl_2/ethanol (98:2) as eluent: yield 0.96 mmol (12%); $[\alpha]^{20}_D$ −44.8° (*c* 1, CH_2Cl_2); mass spectrum, parent *m/e* 207 (theory 207); ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H), 1.9 (m, 2 H), 2.2 (s, 3 H), 2.45 (s, 6 H), 2.85 (m, 7 H). The poor yield is probably the result of competitive cyclization of chloride **11c** to the sulfonium salt; this reaction was not repeated.

(*S*)-2-(Dimethylamino)-1-(phenylthio)-4-(methylthio)butane (12f) was prepared from the chloride **11c** and thiophenol. The product was purified by chromatography over SiO_2 with CH_2Cl_2/ethanol (90:10) as eluent: yield 4.4 mmol (55%); $[\alpha]^{20}_D$ −24.8° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.85 (m, 2 H), 2.05 (s, 3 H), 2.25 (d, 6 H), 2.9 (m, 5 H), 7.25 (m, 5 H); mass spectrum, exact mass *m/e* 255.112 (theory 255.112).

(*S,S*)-4,11-Bis(dimethylamino)-2,6,9,13-tetrathiatetradecane (13) was prepared from the chloride **11b** (9 mmol) and ethanedithiol (4.5 mmol). The product was purified by chromatography over SiO_2 with ether as eluent: yield 2.52 mmol (56%); $[\alpha]^{20}_D$ +23.4° (*c* 3, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 2.15 (s, 6 H), 2.3 (s, 12 H), 2.75 (br m, 14 H); the parent peak was too weak for a mass spectrum.

General Procedure for Preparation of Macrocyclic Sulfides 17a–e. A 2-L three-necked flask was equipped with an addition funnel that could be regulated for slow addition, a stirrer, and a gas line to maintain a nitrogen atmosphere. Cs_2CO_3 (4 mmol) was suspended in 500 mL of dry DMF. To this well-stirred solution held at 45–50 °C was added slowly a solution of the dithiol (3 mmol) and the bis(mesylate) (3 mmol) in 100 mL of DMF. The total time for addition was 12–15 h.

The DMF was removed under vacuum, and the residue was taken up in CH_2Cl_2, washed with H_2O, and dried over $MgSO_4$. Purification was carried out by chromatography over SiO_2 with *n*-hexane/ethyl acetate (3:1) as eluent.

9,10-(1,1-Cyclohexanediyldioxy)-1,4,7-trithiacycloundecane (17a) was prepared from the bis(mesylate) **14** and 3-thiapentane-1,5-dithiol (**15a**): yield 2.4 mmol (80%); $[\alpha]^{20}_{578}$ −11.0° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.60 (br s, 10 H), 2.86 (m, 12 H), 4.10 (m, 2 H); mass spectrum, exact mass *m/e* 320.095 (theory 320.094).

12,13-(1,1-Cyclohexanediyldioxy)-1,4,7,10-tetrathiacyclotetradecane (17b) was prepared from **14** and 3,6-dithiaoctane-1,8-dithiol (**15b**): yield 1.14 mmol (38%); $[\alpha]^{20}_{578}$ −13.2° (*c* 1, $CHCl_3$); ^1H NMR δ 1.60 (br s, 10 H), 2.88 (m, 16 H), 4.3 (m, 2 H); mass spectrum, exact mass *m/e* 380.096 (theory 380.097).

13,14-(1,1-Cyclohexanediyldioxy)-1,4,8,11-tetrathiacyclopentadecane (17c) was prepared from **14** and 3,7-dithianonane-1,9-dithiol (**15c**): yield 1.8 mmol (60%); mass spectrum, parent *m/e* 394 (theory 394); ^1H NMR ($CDCl_3$) δ 1.60 (br s, 10 H), 1.9 (m, 2 H), 2.85 (m, 16 H), 4.05 (m, 2 H).

15,16-(1,1-Cyclohexanediyldioxy)-1,4,7,10,13-pentathiacycloheptadecane (17d) was prepared from **14** and 3,6,9-trithiaundecane-1,11-dithiol (**15d**): yield 2.4 mmol (80%); mass spectrum, parent *m/e* 440 (theory 440); ^1H NMR ($CDCl_3$) δ 1.60 (br s, 10 H), 2.80 (m, 20 H), 4.10 (m, 2 H).

9,10-(1,1-Cyclohexanediyldioxy)-1,4-dioxa-7,12-dithiacyclotetradecane (17e) was prepared from **14** and 3,6-dioxaoctane-1,8-dithiol (**15e**): yield 0.9 mmol (30%); $[\alpha]^{20}_D$ −46.9° (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.55 (br s, 10 H), 2.8 (m, 8 H), 3.6 (m, 10 H); mass spectrum, exact mass *m/e* 348.144 (theory 348.143).

3,4-(1,1-Cyclohexanediyldioxy)-1,6-bis(4-tolylsulfonyl)-1,6-diazacyclohexadecane (18a) was prepared as previously described[14] from 1,10-bis[(*p*-tolylsulfonyl)amino]decane (**16a**) and **14**.

9,10-(1,1-Cyclohexanediyldioxy)-1,4,7-tris(4-tolylsulfonyl)-1,4,7-triazacycloundecane (18b) was prepared from *N,N',N''*-tris(*p*-tolylsulfonyl)diethylenetriamine[34] and **14**, which were added dropwise over 4–5 h to the Cs_2CO_3/DMF mixture, as described above for the macrocyclic sulfides. After workup the product was purified by flash chromatography over SiO_2 with CH_2Cl_2/ethyl acetate (94:6) as eluent: yield 1.2 mmol (40%); $[\alpha]^{20}_D$ −10.2° (*c* 0.9, CH_2Cl_2); mass spectrum, parent *m/e* 731 (theory 731); mol wt (osmometric in $CHCl_3$) 739.6, 749.9 (theory 731.9); ^1H NMR ($CDCl_3$) δ 1.6 (br s, 10 H), 2.4 (s, 9 H), 3.4 (m, 12 H), 4.5 (m, 2 H), 7.5 (m, 12 H); mass spectrum, exact mass *m/e* 576.221 (theory 576.220) for the parent peak minus $CH_3C_6H_4SO_2$. The parent peak was too weak for exact mass determination.

(2*S*,7*S*)-2,7-Dibenzyl-1,8-dimethoxy-3,6-diazaoctane-1,4,5,8-tetrone (19a). To a cooled (ice/salt, −5 °C), stirred solution of L-phenylalanine methyl ester (17.9 g, 100 mmol) and an excess of $(C_2H_5)_3N$ in CH_2Cl_2 (300 mL) was added slowly a solution of oxalyl chloride (50 mmol) in CH_2Cl_2 (30 mL). The temperature was kept below 0 °C. The solution was allowed to come to room temperature. The CH_2Cl_2 was washed with water, 1 N HCl, and brine, respectively. After evaporation of the solvent, the crude yellow solid was recrystallized from ethyl acetate to give **19a**: 18.5 g, 45 mmol (90% yield); mp 196 °C; $[\alpha]^{20}_D$ +77.7° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 3.13 (d, 4 H), 3.67 (s, 6 H), 4.80 (m, 2 H), 7.20 (m, 10 H), 7.78 (br d, 2 H). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.06; H, 5.87; N, 6.79. Found: C, 64.03; H, 6.01; N, 6.71.

(2*S*,9*S*)-2,9-Dibenzyl-1,10-dimethoxy-3,8-diazadecane-1,4,7,10-tetrone (19b) was prepared as described above from L-phenylalanine methyl ester (17.9 g, 100 mmol) and succinyl chloride (50 mmol). Recrystallization from ethyl acetate/diethyl ether gave 16.3 g (37 mmol, 74% yield) of the product as white crystals: mp 138 °C; $[\alpha]^{20}_D$ +88.8° (*c* 0.92, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 2.47 (s, 4 H), 3.08 (d, 4 H), 3.68 (s, 6 H), 4.85 (m, 2 H), 6.70 (d, 2 H), 7.23 (br s, 10 H); mass spectrum, exact mass *m/e* 440.195 (theory 440.195).

(2*S*,10*S*)-2,10-Dibenzyl-1,11-dimethoxy-6-oxa-3,9-diazaundecane-1,4,8,11-tetrone (19c) was prepared as described above from L-phenylalanine methyl ester (17.9 g, 100 mmol) and diglycolic acid chloride (50 mmol). Recrystallization from CCl_4 gave 15.5 g (34 mmol, 68% yield) of the product as white crystals: mp 126 °C; $[\alpha]^{20}_D$ +60.6° (*c* 0.88, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 3.1 (d, 4 H), 3.68 (s, 6 H), 3.95 (s, 4 H), 4.85 (m, 2 H), 6.80 (d, 2 H), 7.20 (br s, 10 H); mass spectrum, exact mass *m/e* 456.189 (theory 456.190).

(*S,S*)-2,7-Dibenzyl-3,6-diaza-1,8-octanediol (20a). To a cooled, stirred suspension of $LiAlH_4$ (75 mmol) in 150 mL of dry THF was added 10.3 g (25 mmol) of **19a** in small portions. The mixture was refluxed for one night. After cooling, 150 mL of diethyl ether was added and thereafter a saturated NaCl solution in water was added dropwise until a white solid resulted, which was filtered with a P3 glass filter. The ether/THF was washed once with water and dried over $MgSO_4$. After filtration and evaporation of the solvent, the crude product **20a** was recrystallized from $CHCl_3$: 5.35 g, 16.3 mmol (65% yield); mp 94 °C; $[\alpha]^{20}_D$ −10.0° (*c* 1.08, absolute EtOH); mass spectrum, parent *m/e* 329 (parent + 1), 164 (100% peak, which arises from half of the symmetric molecule); ^1H NMR ($CDCl_3$) δ 2.28 (br s, 4 H), 2.70 (br m, 10 H), 3.48 (m, 4 H), 7.23 (br s, 10 H). Anal. Calcd for $C_{20}H_{28}N_2O_2 \cdot CHCl_3$: C, 56.31; H, 6.53; N, 6.26; Cl, 23.75. Found: C, 56.46; H, 6.70; N, 6.16; Cl, 23.49.

(*S,S*)-2,9-Dibenzyl-3,8-diaza-1,10-decanediol (20b) was prepared from **19b** as described above. The crude product was

(34) Atkins, T. J.; Richman, J. E.; Oettle, W. F. *Org. Synth.* **1978**, *58*, 86.

recrystallized from diethyl ether/absolute ethanol, which gave 7.75 g (21.8 mmol, 87% yield) of **20b**: mp 74 °C; $[\alpha]^{20}_D$ −14.0° (*c* 1, absolute EtOH); ^{1}H NMR $CDCl_3$) δ 1.4 (m, 4 H), 2.5 (m, 14 H), 3.5 (m, 4 H), 7.25 (br s, 10 H).

(*S*,*S*)-2,10-Dibenzyl-3,9-diaza-6-oxa-1,11-undecanediol (20c) was prepared from **19c** as described above. The crude product was recrystallized from diisopropyl ether, which gave 5.2 g (13.9 mmol, 56% yield) of **20c**: mp 98 °C; $[\alpha]^{20}_D$ −4.3° (*c* 0.8, absolute EtOH); ^{1}H NMR ($CDCl_3$) δ 2.7 (m, 14 H), 3.45 (m, 8 H), 7.26 (s, 10 H). Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.93; H, 8.66; N, 7.52. Found: C, 70.51; H, 8.65; N, 7.52.

General Procedure for Preparing the Macrocycles with *N*-Ethyl Substituents. This is illustrated for (3*S*,8*S*)-3,8-dibenzyl-4,7-diethyl-4,7-diaza-1,10-dithiacyclododecane (**21a**). To a cooled, stirred solution of 3.28 g (10 mmol) of **20a** and 50 mmol of $(C_2H_5)_3N$ in 75 mL of CH_2Cl_2 was added slowly a solution of 40 mmol of acetyl chloride in 25 mL of CH_2Cl_2. The solution was allowed to come to room temperature and stirred for 1 h. The organic layer was washed with water, 1 N HCl, and brine, respectively. After drying over $MgSO_4$, followed by filtration and evaporation, the product was put in 30 mL of dry THF and slowly added to a cooled suspension of 50 mmol of $LiAlH_4$ in THF. The mixture was refluxed for one night. After cooling, 100 mL of diethyl ether was added and the same workup procedure was followed as described for the reduction of the compounds **19a–c** to give the *N*-ethylamino alcohol, which was directly used in the chlorination step because of air sensitivity.[35] ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 6 H), 2.8 (br m, 20 H), 7.23 (br s, 10 H). The product was dissolved in 15 mL of C_2H_5OH, 2 mL of concentrated HCl added, and the solvent evaporated to dryness. The dihydrochloride salt was dissolved in 30 mL of dry $CHCl_3$ and the resultant mixture cooled. Thionyl chloride (30 mmol) was slowly added and the mixture refluxed 2 h. After evaporation, $CHCl_3$ was added and evaporated two times. The corresponding dichloride (dihydrochloride salt) was used without further purification in the ring-closure step. This step was slightly different from the one mentioned for the macrocyclic sulfides. A mixture was of 5 mmol of the freshly prepared chloride and 5 mmol of 1,2-ethanedithiol in 250 mL of dry DMF, under a nitrogen atmosphere, was added to a suspension of 20 mmol of Cs_2CO_3 in dry DMF over a period of 12–15 h, at 50 °C. The DMF was removed under vacuum. The crude product was taken up in 1 N HCl and washed with ether. After neutralization with $NaHCO_3$ to pH 7 the water layer was extracted three times with $CHCl_3$. The combined $CHCl_3$ layers were dried over $MgSO_4$. After filtration and evaporation the crude product was purified by flash chromatography over Kieselgel (Merck 60, 230–400 mesh ASTM, column length ~30 cm × 25 mm) using *n*-hexane/ethyl acetate (2:1) as eluent. The product **21a** was obtained: 450 mg, 1 mmol (20% yield); $[\alpha]^{20}_D$ −91.6° (*c* 2.5, $CHCl_3$); mass spectrum, *m*/*e* 351 (100%, molecular ion minus benzyl), 443 (2.2%, parent ion + 1); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 6 H), 2.8 (br m, 22 H), 7.23 (s, 10 H). The parent peak was too weak for an exact mass determination.

(3*S*,8*S*)-3,8-Dibenzyl-4,7-diethyl-4,7-diaza-1,10-dithiacyclotridecane (21b) was prepared as described for **21a**: yield 593 mg, 1.3 mmol (26% yield); $[\alpha]^{20}_D$ 51.4° (*c* 3, $CHCl_3$); mass spectrum, *m*/*e* 365 (100%, molecular ion minus benzyl), 456 (0.9%, parent), 457 (0.4%, parent + 1); ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 6 H), 1.85 (br m, 2 H), 2.5 (br m, 22 H), 7.23 (s, 10 H); mass spectrum, exact mass *m*/*e* 456.263 (theory 456.263).

(3*S*,8*S*)-3,8-Dibenzyl-4,7-diethyl-4,7-diaza-1,10-dithiacyclotetradecane (21c) was prepared as described above: yield 588 mg, 125 mmol (25% yield); $[\alpha]^{20}_D$ 101.4° (*c* 0.7, $CHCl_3$); mass spectrum, *m*/*e* 379 (100%, molecular ion minus benzyl), 470 (1.1%, parent), 471 (0.6%, parent + 1); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 6 H), 1.72 (br m, 4 H), 2.6 (br m, 22 H), 7.23 (s, 10 H); mass spectrum, exact mass *m*/*e* 379.224 (theory 379.221) of the 100% peak. The parent peak was too weak for an exact mass determination.

(3*S*,10*S*)-3,10-Dibenzyl-4,9-diethyl-4,9-diaza-1,2-dithiacyclopentadecane (21d) was prepared as described above: yield 751 mg, 1.55 mmol (31% yield); $[\alpha]^{20}_D$ −18.5° (*c* 2, $CHCl_3$); mass spectrum, *m*/*e* 393 (100%, molecular ion minus benzyl); ^{1}H NMR ($CDCl_3$) δ 1.1 (t, 6 H), 1.6 (m, 6 H), 2.65 (m, 22 H), 7.25 (s, 10 H). The parent peak was too weak for an exact mass determination.

General Procedure for N-Methylation. This is illustrated for (3*S*,10*S*)-3,10-dibenzyl-4,9-dimethyl-4,9-diaza)-1,12-dithiacyclopentadecane (**21e**). To 3.56 g (10 mmol) of **20b** was added 12 mL of formic acid and 6 mL of formaldehyde (37 wt % solution in water). The mixture was stirred and refluxed for one night. After cooling to 40 °C, 15 mL of concentrated HCl was added and the mixture stirred for 2 h at room temperature. After cooling, the mixture was made basic (pH 11) with concentrated NaOH and extracted several times with CH_2Cl_2. The CH_2Cl_2 layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The resulting crude product was purified by flash chromatography over SiO_2 with CH_2Cl_2/CH_3OH (75:25) as eluent and directly used in the chlorination step as described for **21a–d**: ^{1}H NMR ($CDCl_3$) δ 1.6 (m, 4 H), 2.4 (s, 6 H), 2.8 (br m, 14 H), 4.6 (br m, 2 H), 7.23 (br s, 10 H). Also the ring-closure step is analogous to that described for **21a–d**, prepared on 5-mmol scale. Purification after workup was carried out by flash chromatography over SiO_2 using *n*-hexane/ethyl acetate (1:1) as eluent: yield 365 mg, 0.8 mmol (16% yield); $[\alpha]^{20}_D$ −14.7° (*c* 1, CH_2Cl_2); mass spectrum, *m*/*e* 365 (100%, molecular ion minus benzyl), 456 (0.7%, parent); ^{1}H NMR ($CDCl_3$): δ 1.6 (m, 6 H), 2.27 (s, 6 H), 2.6 (m, 18 H), 7.23 (br s, 10 H); mass spectrum, exact mass *m*/*e* 456.262 (theory 456.263).

(5*S*,18*S*)-5,18-Dibenzyl-4,19-dimethyl-4,19-diaza-7,10,13,16-tetrathia-1-oxacycloheneicosane (21f) was prepared as described above: yield 608 mg, 1.05 mmol (21% yield); $[\alpha]^{20}_D$ −6.3° (*c* 1, $CHCl_3$); mass spectrum, *m*/*e* 487 (100%, molecular ion minus benzyl), 578 (12.1%, parent); ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 6 H), 2.8 (br m, 30 H), 7.23 (br s, 10 H); mass spectrum, exact mass *m*/*e* 578.247 (theory 578.249).

(6*S*,13*S*)-6,13-Bis(dimethylamino)-1,4,8,11-tetrathiatetradecane (24). To a solution of 800 mL of H_2O and 80 mL of C_2H_5OH was added 24.2 g (200 mmol) of L-cysteine, 16.8 g (200 mmol) of $NaHCO_3$, and 18.8 g (100 mmol) of 1,2-dibromoethane. The mixture was stirred and heated at 70–90 °C for 1 h. After cooling, the white precipitate was filtered, washed with cold water, and dried to give 26.8 g (108 mmol, quantitative conversion)[36] of not completely dry diacid, which was added to a mixture of 100 mL of H_2O, 50 mL of formaldehyde (37 wt % solution in water), and 5 g of 10% Pd on charcoal and shaken for one night under hydrogen atmosphere in a Parr apparatus. The mixture was diluted with 50 mL of C_2H_5OH and then heated and filtered over a P4 glass filter. The solvent was removed under vacuum and the crude (2*S*,9*S*)-2,9-bis(dimethylamino)-4,7-dithia-1,10-decanedicarboxylic acid was recrystallized from C_2H_5OH/H_2O to give 25.95 g (80 mmol, 80% yield) of product: $[\alpha]^{22}_D$ 93.3° (*c* 1, H_2O); ^{1}H NMR (D_2O) δ 2.3 (s, 4 H), 2.35 (s, 12 H), 2.6 (d, 4 H), 3.27 (t, 2 H).

This acid (16.2 g, 50 mmol) was added in portions to a suspension of $LiAlH_4$ (100 mmol) in 200 mL of dry THF. After reflux for one night the mixture was worked up as previously described for the other reductions, to give 8.9 g (30 mmol, 60% yield) of the diol **23a**: $[\alpha]^{22}_D$ 45.2° (*c* 1.4, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 12 H), 2.75 (m, 12 H), 3.55 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 64.08, 59.58, 39.80, 32.00, 27.44.

The chlorination step was carried out as described for compounds **21**. Care should be taken not to raise the temperature above 50 °C when $CHCl_3$ is evaporated. The chloride is very sensitive to rearrangement and hence was used immediately. The cyclization step of the chloride and 1,4-butanedithiol was carried out at 40 °C. After the usual workup the crude compound was put on a column for flash chromatography. Hexane/ethyl acetate (1:2), ethyl acetate, and finally ethyl acetate/methanol (95:5) were used as eluent. The compound isolated this way contains small fractions of dimer, which can be seen as a small extra singlet for the NMe_2 absorption in the proton NMR next to the singlet for monomeric material. This was confirmed by osmometric molecular weight determinations, which consistently gave high values for these fractions. The measured molecular weights agreed within 5% with those calculated from the composition established by NMR spectroscopy.

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(36) Zahn, H.; Traumann, K. *Justus Liebig's Ann. Chem.* **1953**, *581*, 168.

This product was subjected to preparative HPLC (Waters Associates, ethyl acetate/MeOH (60:40) as eluent) which gave the pure monomer. However, on checking rotations of different runs of cyclizations we found different values for [α]. Using again the HPLC system but now with CH_3OH and 0.5% $(C_2H_5)N$, we were able to separate the optically active pure monomer and the meso compound: yield 153 mg, 0.4 mmol (8% yield); $[\alpha]^{21}_D$ −89° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.73 (m, 4 H), 2.30 (s, 12 H), 2.66 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 64.15, 40.70, 32.53, 32.34, 32.24, 31.62, 28.17; mass spectrum, exact mass m/e 382.160 (theory 382.160). Purification was also achieved on a reversed-phase column (Rhodorsyl C8) with water/CH_3OH (10–40% water) and 0.5% CF_3COOH as eluent: ^1H NMR of the bis(trifluoroacetate) salt ($CDCl_3$) δ 1.81 (br s, 4 H), 2.74 (m, 4 H), 2.91 (s, 12 H), 2.95 (m, 12 H), 3.72 (m, 2 H).

2,5,9,12-Tetrathiatridecane (25) was prepared on 5-mmol scale analogously to ref 13 from dithianonane-1,9-dithiol and methyl iodide: yield 95%; ^1H NMR ($CDCl_3$) δ 1.90 (m, 2 H, CH_2), 2.10 (s, 6 H, SCH_3), 2.70 (t, 4 H, CH_2CH_2S), 2.75 (s, 8 H, CH_2S).

Cross-Coupling Reactions. The synthesis of the Grignard reagent of 1-phenyl-1-chloroethane was carried out by two different procedures. Method A: In $(C_2H_5)_2O$ (50 mL) was dissolved 1-phenyl-1-chloroethane (8.4 g, 60 mmol) and the resultant mixture added dropwise to a suspension of freshly activated Mg turnings (1.58 g, 65 mmol) in 50 mL of $(C_2H_5)_2O$; the reaction was started with a crystal of I_2 and held at 0–5 ° during addition of the chloride. The entire Grignard solution was decanted from the unreacted turnings into an addition funnel. The Grignard suspension was added to a suspension of $NiCl_2$ (0.4 mmol), ligand (0.4 mmol), and vinyl bromide (5.36 g, 50 mmol) in $(C_2H_5)_2O$ (10 mL). The Grignard suspension was added at such a rate that the temperature did not rise above −40 °C. The entire solution was stirred magnetically and held under constant N_2 pressure. After addition the solution was allowed to come to 0 °C over a period of 16 h and to room temperature for 1 h. The reaction mixture was hydrolyzed at 0 °C with 1 N HCl solution (50 mL). The resulting mixture was poured into a separatory funnel and the flask rinsed with $(C_2H_5)_2O$ (50 mL). The aqueous HCl layer was drawn off, and the ether layer was again washed with 1 N HCl solution (40 mL) and water. The ether layer was dried over $MgSO_4$. After removal of the solvent the crude material was distilled [bp 90–110 °C (30 torr)], and the sample was then analyzed by ^1H NMR spectroscopy and polarimetry; analytically pure product was obtained by preparative GLC.

Method B differs in the preparation of the Grignard reagent, which was now prepared on a 500-mmol scale as described above. The solid materials were allowed to settle, and then the supernatant solution was removed by syringe prior to reaction, which was carried out as described above.

In both methods an aliquot of the Grignard reagent was removed, hydrolyzed with 1 N HCl solution, and then back-titrated with base. The ratio of Grignard to vinyl bromide in method A is 0.8 to 1. In the case of method B a Grignard to vinyl bromide ratio of 2:1 is used.

Registry No. **2**, 672-65-1; **3**, 593-60-2; **4**, 61474-21-3; **5**, 61045-33-8; **5** (diamide), 105206-81-3; **5** (diamine), 105206-82-4; **6**, 90633-68-4; **7**, 105206-80-2; **8**, 105206-84-6; **8** (amide), 105206-83-5; **9**, 105307-25-3; **9** (dithiol), 68170-33-2; **11a**, 105206-90-4; **11e**, 105206-91-5; **11c**, 105206-92-6; **12a**, 90633-69-5; **12b**, 105206-85-7; **12c**, 105206-86-8; **12d**, 105206-87-9; **12e**, 105206-88-0; **12f**, 105206-89-1; **13**, 90633-71-9; **14**, 87338-21-4; **15a**, 3570-55-6; **15b**, 25423-55-6; **15c**, 25676-62-4; **15d**, 60147-09-3; **15e**, 14970-87-7; **16a**, 79130-37-3; **16b**, 56187-04-3; **17a**, 105206-93-7; **17b**, 90633-72-0; **17c**, 105206-94-8; **17d**, 105206-95-9; **17e**, 105229-63-8; **18a**, 87338-20-3; **18b**, 105206-96-0; **19a**, 105206-97-1; **19b**, 95954-69-1; **19c**, 105229-64-9; **20a**, 103747-96-2; **20b**, 103747-98-4; **20c**, 103747-99-5; **21a**, 103747-89-3; **21b**, 105206-99-3; **21c**, 103747-91-7; **21d**, 103747-92-8; **21e**, 103747-93-9; **21f**, 103747-94-0; **22**, 52-90-4; **23a**, 103748-00-1; **23a** (diacid), 105229-65-0; **24**, 103747-95-1; **25**, 105207-00-9; C_2H_5SH, 75-08-1; C_6H_5SH, 108-98-5; CH_3I, 74-88-4; $C_6H_5CH_2SH$, 100-53-8; (L)-$C_6H_5CH_2CH(NH_2)CO_2CH_3$, 2577-90-4; ClCOCOCl, 79-37-8; $ClCO(CH_2)_2COCl$, 543-20-4; $ClCOCH_2OCH_2COCl$, 21062-20-4; $Br(CH_2)_2Br$, 106-93-4; $HS(CH_2)_2SH$, 540-63-6; $HS(CH_2)_4SH$, 1191-08-8; $NiCl_2$, 7718-54-9.

Diels–Alder Reactions of Cycloalkenones. 11. Regioselectivity of 2-Cyclohexenones[1]

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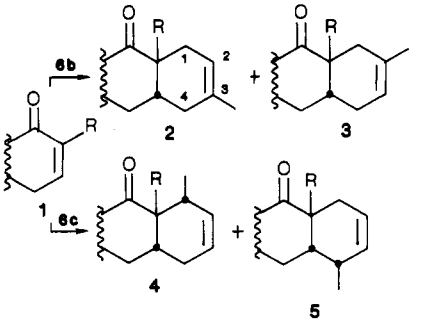
The Diels–Alder reactions of isoprene and 2-methyl-1,3-pentadiene with 2,4-dimethyl-, 4,4-dimethyl-, and 5,5-dimethyl-2-cyclohexenone and 2,4,4-trimethyl-, 2,5,5-trimethyl-, and 2,6,6-trimethyl-2-cyclohexenone under aluminum chloride catalysis are described. Structure analysis of the adducts by NMR spectroscopy is presented. The relationship between the *gem*-dimethyl site and the regioselectivity and diastereoselectivity of the cycloadditions is discussed.

In principle, the Diels–Alder reaction of an unsymmetrical diene and/or dienophile can lead to two regioisomeric adducts, e.g., the reactions of ketone 1 with isoprene (**6b**) or (*E*)-piperylene (**6c**) (Scheme I). The Lewis acid catalyzed cycloadditions of alkylated 2-cyclohexenones and these dienes, however, have shown high regioselectivity in favor of adducts of types **2** and **4**, respectively,[3] in accord with frontier molecular orbital theory.[4] An exception has been the reaction of 4,4-dimethyl-2-cyclohexenone (**7a**)

Scheme I



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