L-Cysteine-, L-Methionine-, and D-Penicillamine-Derived Ligands for Transition Metal Catalyzed Carbon–Carbon Bond-Forming Reactions

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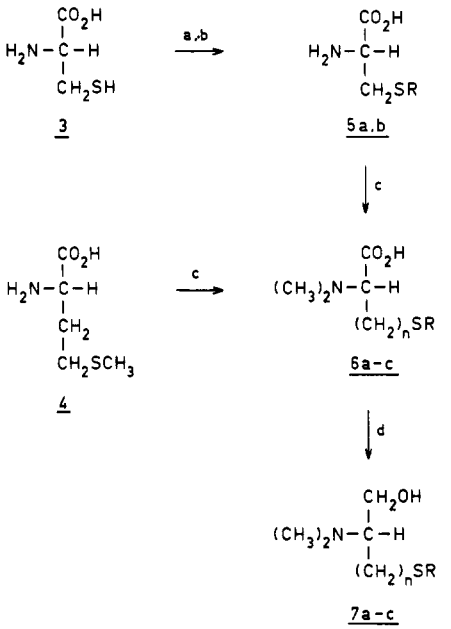
Synthetic methods are described for the conversion of L-cysteine, L-methionine, and D-penicillamine to S-alkylated dimethylamino alcohols derived by, respectively, alkylation of sulfur and nitrogen followed by reduction of the carboxyl group. One-pot mesylation followed by treatment with lithium diphenylphosphide provides the corresponding phosphine derivative, 2-(dimethylamino)-1-(diphenylphosphino)-3-(methylthio)propane (cysphos), the *S*-isopropyl derivative (isopropylcysphos), 2-(dimethylamino)-1-(diphenylphosphino)-4-(methylthio)butane (methphos), and 2-(dimethylamino)-1-(diphenylphosphino)-3-methyl-3-(methylthio)butane (penphos). The latter ligand had an enantiomeric excess of 82%, whereas the other ligands are enantiomerically pure. These compounds have been used as ligands for the solubilization of catalytic amounts of $NiCl_2$, which is used to mediate the coupling of vinyl bromide with the (racemic) Grignard reagent of 1-phenyl-1-chloroethane. The coupling product, 3-phenyl-1-butene, is formed in excellent yields and with enantiomeric excesses of up to 65% (methphos). In addition the cross coupling of vinyl bromide to the Grignard reagent of 2-octyl chloride has also been examined; enantiomeric excesses of 3-methyl-1-nonene of up to 18% are obtained (penphos). Some comments regarding mechanism and the possible effect of the sulfur heteroatom are made. In addition it is shown that the method of preparation of the Grignard reagent and the concentration thereof are important considerations for the overall enantiomeric excess of the derived coupling product.

We have shown that various chiral ligands, which contain sulfur or sulfur/nitrogen combinations of heteroatoms, can be used in Ni(II)-catalyzed sp^2–sp^3 bond forming reactions.[2,3] The general type of reaction under consideration as depicted in eq 1 involves coupling of a racemic

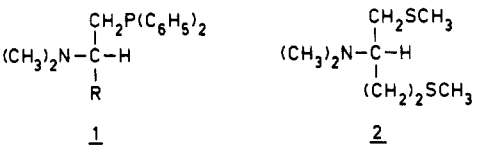
$$\underset{\text{(or aryl)}}{\text{RMgX + vinyl-X'}} \xrightarrow[\text{catalytic}]{\text{NiCl}_2\text{-ligand}} \underset{\text{(or aryl)}}{\text{vinyl-R}} + \text{MgX,X'} \qquad (1)$$

secondary Grignard reagent with a vinyl halide. This type of reaction has been studied in detail by Kumada[4] and Consiglio.[5] Various types of optically pure phosphine-based ligands have been developed by these groups, and the enantiomeric excesses of the coupling products are on occasion in the 80–90% range. *Non*phosphine-derived ligands synthesized by us,[2a,b] both open chain and macrocyclic, have led also to excellent yields of products but with enantiomeric excesses no greater than 17%.[2a,b] In several cases these ligands were derived from the sulfur-containing amino acid L-cysteine. In the course of examination of this and other sulfur-containing amino acids (L-methionine and D-penicillamine) we found it advisable to prepare from these amino acids also *phosphine*/amine ligands, following the line set by Kumada et al.,[4] who have studied extensively the transformations of various amino acids to ligands of general structure 1 (or the enantiomeric (*R*)-1). R is isopropyl (valphos), isobutyl (leuphos), etc.[4a]

Scheme I[a]



[a] (a) Na, C_2H_5OH; (b) R'I, CH_3CO_2H; (c) HCHO, Pd(C), H_2; (d) $LiAlH_4$, THF.



In this regard we mention that **2**, derived from L-methionine (the corresponding L-cysteine-derived compound is achiral) led also to good yields of coupling product but again with very low enantiomeric excesses.[2b]

We therefore prepared ligands related to **1** but with R groups that contain sulfur and that vary with respect to

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(2) (a) Lemaire, M.; Buter, J.; Vriesema, B. K.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1984**, 309. (b) A macrocyclic ligand that provides much higher ee's has been prepared: Lemaire, M.; Vriesema, B. K.; Kellogg, R. M., *Tetrahedron Lett.*, in press. (c) The need for new types of chiral ligands has been stressed in the recent review by: Kagan, H. B. In "Comprehensive Organometallic Chemistry"; Wilkinson, F. G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, pp 463–498.

(3) General reviews: (a) Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, CA, 1980. (b) 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.

(4) For example: (a) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195. (b) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagobani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180. (c) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fijioka, A.; Kodama, S.-i.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958.

(5) For example: (a) Consiglio, G.; Morandini, F.; Picolo, O. *J. Chem. Soc., Chem. Commun.* **1983**, 112. (b) Consiglio, G.; Morandini, F.; Picolo, O. *Tetrahedron* **1983**, *39*, 2699.

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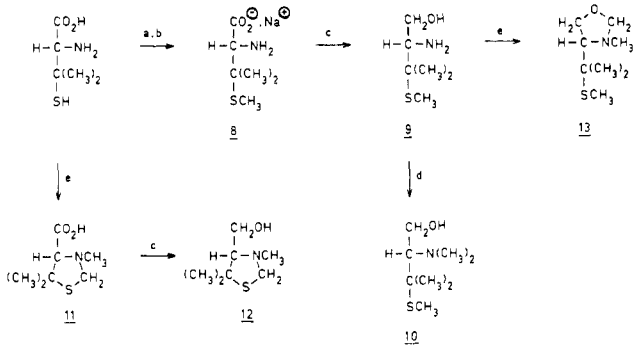
Scheme II[a]



[a] (a) Na, C_2H_5OH; (b) CH_3I; (c) $LiAlH_4$, THF; (d) HCHO, HCO_2H; (e) HCHO, H_2, Pd(C).

chain branching. The syntheses and reactions of these compounds are described here in detail.

Results

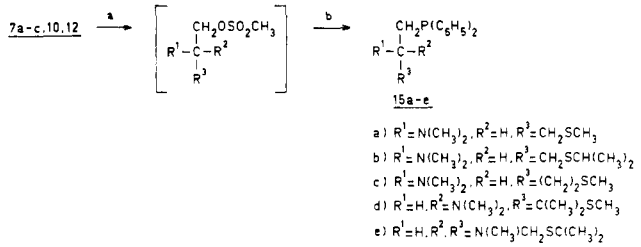
A. Synthesis. The syntheses of the amino alcohols **7** followed literature precedent and are outlined in Scheme I. Fischer projections are used in this and other schemes. The enantiomeric purities of **7a** and **7c** were established to be 100% by preparation, in the former caseof the Mosher derivative[6] and for **7c** by analysis with $Eu(hfc)_3$. There was extra concern in the case of **7c**, owing to variations in the rotations found for different preparations. The possibility of partial racemization was excluded, however. The pertinent experiments are described in the Experimental Section.

Preparation of **10** from commercially available D-penicillamine was more difficult. As shown in Scheme II methylation of the amine functionality was carried out *after* reduction of the carboxyl group. Direct methylation afforded **8** when the literature procedure for alkylation of cysteine was followed.[7] Unfortunately, neither the acid form nor the salt of **8** could be obtained free of iodide, which poisons the Pd(C) catalyst required for alkylation of nitrogen as in the **5** to **6** conversion.[8] Reduction of the salt of **8** to **9** took place smoothly, however, and **9** could be purified. Methylation of the amine functionality at this stage was accomplished by means of the Eschweiler–Clark reaction. The rotations of **10** were also dependent on the batch. Conversion to the Mosher ester and analysis by ^{19}F NMR established that the batch for **10** to be converted to penphos (see further) had an enantiomeric excess of 82% of what surely must be the *S* enantiomer. We suspect that partial racemization occurs at the stage of the Eschweiler–Clark alkylation of amino alcohol **9** although this has neither been proven nor have exhaustive attempts been made to avoid racemization.

A side reaction noted was the formation of **13** on attempted dimethylation of **9** by means of catalytic reduction in the presence of formaldehyde. Application of this same methodology at the stage of the amino acid led to thiazolidine **11**, which was reduced to **12**. This material was used as described subsequently.

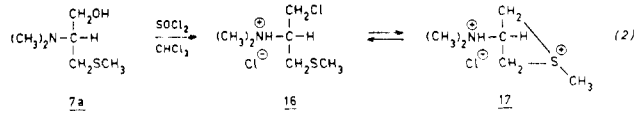
The ligands **15a–e** were prepared as shown in Scheme III. The methodology differs quite considerably from that described by Kumada et al.[4a] These authors converted the dimethylamino alcohols obtained as shown in Scheme I to the chlorides (as hydrochloride salts) with $SOCl_2$. This reaction, which works well indeed with compounds like

Scheme III[a]



[a] (a) CH_3SO_2Cl, proton sponge, THF; (b) $(C_6H_5)_2PH$, 2.5 equiv $KOC(CH_3)_3$, THF, 0–25 °C.

(dimethylamino)valinol, when applied to, for example, **7a**, as shown in eq 2, leads to **16**, which is extremely sensitive,



likely owing to formation of thietanium ion **17**.[9] If **17** is formed reversibly, the consequence will be racemization of **16**. A means of minimizing this problem was found in a one-pot procedure, which provides an efficient manner of obtaining the desired products **15**, albeit in only modest yields. Mesylation (instead of chlorination) was carried out in THF with excess 1,8-bis(dimethylamino)-naphthalene, "proton sponge", to generate the mesylate as the *free amine*. To this crude mixture was added potassium diphenylphosphide in THF, formed by deprotonation of diphenylphosphine with potassium *tert*-butoxide; a sufficient excess of potassium *tert*-butoxide was present to neutralize all protonated proton sponge. After workup and Kugelrohr distillation **15a–e** were obtained in 20–30% yield based on starting alcohol; considerable amounts of unreacted alcohol were usually recovered, however. All of the phosphines are highly sensitive to oxygen and must be stored in the cold in an inert atmosphere. Compound **15e** had spectra consistent with the proposed structure, but satisfactory analytical data could not be obtained, apparently because of some unidentified residual impurity.

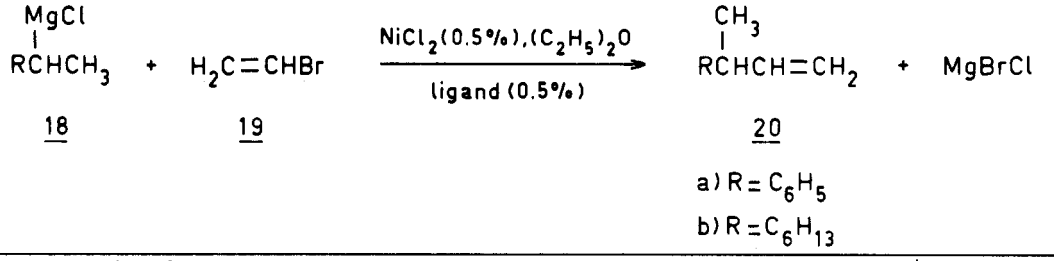
B. Cross-Coupling Reactions. The general reaction illustrated in eq 1 (also heading Table I) was carried out with the ligands prepared. The Grignard reagents of (racemic) 1-phenylethyl chloride and 2-chlorooctane were coupled with vinyl bromide under the conditions described in the Experimental Section. We found that the method of preparation of the Grignard reagent has a significant effect on the enantiomeric excess (ee) of the product **20**. Method A (Table I) refers to Grignard reagent prepared from alkyl chloride and magnesium with activation by iodine; the solution is subsequently decanted from unreacted magnesium. Method B differs in that the Grignard reagent is allowed to stand and then the clear solution is removed from the precipitate, which consists of unreacted magnesium and magnesium halides. In the latter case more dialkylmagnesium should be present.[10] The Grig-

(6) Dale, J. A.; Duff, D. L.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 3245.
(7) Theodoropoulous, D. *Acta Chem. Scand.* **1959**, *13*, 383.
(8) Bowman, R. E.; Stroud, H. H. *J. Chem. Soc.* **1950**, 1342.

(9) Chlorides like **16** can be prepared, of course, but the presence of the unprotected sulfur (the amine functionaility is, of course, protected as the HCl salt) sets close experimental limits within which one must work. Anchimeric participation of sulfur via 1,3-interaction (cysteinol) or 1,4-interactions (methioninol) is, of course, well documented and has been encountered regularly by us in related work: Lemaire, M.; Strijtveen, B., unpublished results.

(10) For a comprehensive review of the properties of Grignard reagents and the consequences of the Schlenk equilibrium, see: Lindsell, W. E. In "Comprehensive Organometallic Chemistry"; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 1, pp 156–187.

Table I. Asymmetric Nickel-Catalyzed Cross Coupling of Grignard Reagents with Vinyl Bromide



18 19 20

a) R = C_6H_5

b) R = C_6H_{13}

entry	ligand	R	A/B	method[a]	ee, % [config][b]	yield,[c] %
1	**15a**	C_6H_5	2	A	23 [*S*]	>90
2	**15a**	C_6H_5	2	B	38 [*S*]	>90
3	**15a**	n-C_6H_{13}	2	B	5 [*R*]	46
4	**15b**	C_6H_5	2	A	22 [*S*]	>90
5	**15b**	C_6H_5	2	B	37 [*S*]	>90
6	**15b**	n-C_6H_{13}	2	B	3 [*R*]	47
7	**15c**	C_6H_5	2	A	46 [*S*]	>90
8	**15c**	C_6H_5	1	A	54 [*S*]	>90
9	**15c**	C_6H_5	2	B	65 [*S*]	>90
10	**15c**	n-C_6H_{13}	2	B	7 [*R*]	49
11	**15d**	C_6H_5	2	A	42 (51)[d] [*R*]	>90
12	**15d**	C_6H_5	2	B	40 (48)[d] [*R*]	>90
13	**15d**	n-C_6H_{13}	2	B	14 (18)[d] [*S*]	45
14	**15e**	C_6H_5	2	A	20 [*R*]	>90
15	**15e**	C_6H_5	2	B	38 [*R*]	>90
16	**15f**	C_6H_5	2	A	28 [*S*]	>90
17	**15f**	C_6H_5	2	B	59 [*S*]	>90
18	**15f**	n-C_6H_{13}	2	B	3 [*R* (4)]	69

[a] Methods A and B are described in the Experimental Section together with the procedures for cross-coupling reactions. [b] For enantiomerically pure (*R*)-3-phenyl-1-butene a value of $[\alpha]^{20}_D$ −5.91° (1 dm, neat) was used.[4b] For enantiomerically pure 3-methyl-1-nonene a value of $[\alpha]^{20}_D$ +14.6° (1 dm, neat) was used.[4b] The ee's of 3-phenyl-1-butene were reproducible to ±3% and those of 3-methyl-1-nonene to ±1%, based on reactions run at a minimum in duplicate. All enantiomeric excesses are calculated from the distilled products and are corrected for small amounts of residual ethyl benzene, styrene, and/or octane. [c] Yields of 3-phenyl-1-butene determined from ^{1}H NMR spectra of crude product mixtures. The isolated yields were 60–75%. The yields for 3-methyl-1-nonene are those of isolated material. [d] Corrected for 82% assumed optical purity of this ligand.

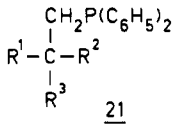
nard reagent from 1-phenylethyl chloride is particularly troublesome because 10–40% coupling always occurs to form the diastereomeric 2,3-diphenylbutanes (and magnesium chloride). Solutions were titrated prior to use to determine the real concentrations. Pertinent results for the coupling reactions are given in Table I.

Discussion

These amino acid derived ligands provide excellent yields of cross-coupling products **20**. The efficiencies, as expressed by the ee, of these *catalytic* reactions lie in the same order as observed by Kumada et al. for non-sulfur-containing amino acids converted to amine/phosphine ligands. There is some ambiguity in this conclusion, however, because we have been unable to obtain as high an ee for valphos (**15f**) as reported by the Kumada group. They have found ee 81% for the formation of **21a** with valphos as the ligand, whereas we have never obtained an ee greater than 60% under any conditions examined. In this connection, we find that the method of preparation of the Grignard reagent has a great effect on the observed ee. For valphos (entries 16 and 17, Table I) the ee more than doubles on use of Grignard reagent freed as well as possible of salts. The same effect, although not so dramatic, was observed with the other ligands listed in the Table (compare entries 1 and 2, entries 4 and 5, entries 8 and 9, and entries 14 and 15). We believe that our inability to reproduce exactly Kumada's reported ee's (although we see the same trends) lies chiefly in experimental approaches to the preparation and handling of the Grignard reagent or the effect of some, as yet undefined, variable that could influence also this quite complicated reaction.[5b,10] We do assume, with reason,[4a,5a,10] that the α-methylbenzyl Grignard reagent racemizes rapidly compared to the rate of cross coupling.

If the above interpretation is correct, then methphos (**15c**) is a good ligand indeed. It gives appreciably higher enantiomeric excesses of 3-phenyl-1-butene (**20a**) than either of the cysphos derivatives or penphos or, in our hands at least, valphos. Although the ee's for 3-methyl-1-nonene (**20b**) are of lesser magnitude, that with penphos (18% corrected) is the best reported to date for this product. One might conclude that a four-carbon bridge between the phosphine and sulfur (or a three-carbon bridge between amine and sulfur) is better than the three-carbon bridges of the cysphos derivatives or penphos. The extra steric encumbrance of the latter ligand must be the cause, however, of improved ee's with respect to cysphos. It is, of course, impossible without stable complexes and accompanying crystallographic data to determine whether the sulfide complexes to the metal at some intermediate stage in these complicated reactions.[3a] We have demonstrated that in non-phosphine-containing systems that sulfur can complex, and we anticipate that crystallographic work in progress will reveal eventually whether this is true in the present examples.

A mechanistic speculation can be advanced, however, for rationalization of the stereochemical results obtained with amine/phosphine ligands derived from amino acids. For **21a–g** and **15e**, synthesized by Kumada et al., as well as **15a–d**, prepared by us, the *S* ligand always gives (*S*)-3-phenyl-1-butene (**20a**) or, for the cases of **20f,g** and **15d,e** the *R* enantiomer synthesized leads to preferential formation of (*R*)-**20a**. This suggests the operation of common stereochemical factors on the pathway leading to product. On the basis of results obtained with stable nickel complexes pertinent to the present examples,[11a,b] it is reason-



21

a) $R^1 = N(CH_3)_2$; $R^2 = H$; $R^3 = CH_3$ [(S)-alaphos]
b) $R^1 = N(CH_3)_2$; $R^2 = H$; $R^3 = i\text{-}C_4H_9$ [(S)-leuphos]
c) $R^1 = N(CH_3)_2$; $R^2 = H$; $R^3 = CH_2C_6H_5$ [(S)-phephos]
d) $R^1 = N(CH_3)_2$; $R^2 = H$; $R^3 = s\text{-}C_4H_9$ [(S)-ilephos]
e) $R^1 = H$; $R^2 = N(CH_3)_2$; $R^3 = C_6H_5$ [(R)-phglyphos]
f) $R^1 = H$; $R^2 = N(CH_3)_2$; $R^3 = t\text{-}C_4H_9$ [(R)-t-leuphos]

able to postulate an unstable intermediate leading to 3-phenyl-1-butene as a square planar cis-substituted diorgano (vinyl and α-methylbenzyl) complex. This is formed by attack of racemic Grignard reagent on **22** (Scheme IV). From consideration of CPK models **23a,b** seem the most reasonable formulations. Of these two diastereomers, **23a**, based on potential interactions of substituents, should be more stable. If reductive elimination, which is expected to be rapid,[11b] takes place with retention of configuration,[13] then **23a** will lead to the observed *S* enantiomer of **20a**. In this interpretation the rate of formation of **23a** is greater than that of **23b**, and both are formed from a pool of 18 that racemizes rapidly.

We stress, however, the speculative nature of this interpretation, which is offered only as a possible rationale for the design of other and better ligand systems. A question that remains to be solved is the possibility that sulfide coordinates to the metal at some stage in the reaction. Also, one should note that the role of the dimethylamine substituents as ligands for nickel and/or as potential coordinating sites for the Grignard reagent, as suggested by Kumada et al.[4a] is anything but clear.

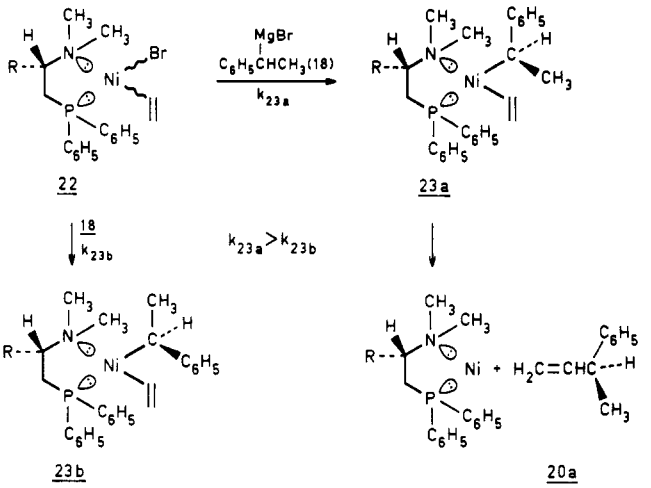
Experimental Section

General. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were obtained with Varian A-60 (60 MHz, cw) or Nicolet (200 MHz) instruments. ^{13}C NMR spectra were obtained at 25.16 MHz on a Varian XL-100 instrument. The reported spectra are proton decoupled; the P–C couplings are given, however, for **15a–e**. Chemical shifts are reported in ppm downfield from Me_4Si. Mass spectral measurements were carried out on an AEI-MS9 instrument operating at 70 eV.

Amino acid starting materials were purchased from Janssen Chemicals. 1-Phenethylchloride was prepared by treating (±)-1-phenethyl alcohol with $SOCl_2$ in $CHCl_3$. 2-Chlorooctane was obtained by treating (±)-2-octanol with $SOCl_2$ in CH_2Cl_2. Other compounds were available from stock. Diphenylphosphine was prepared by the literature procedure.[14] Microanalyses were done by the analytical division of these laboratories.

***S*-Alkylcysteine Derivatives 5a,b.** The reported procedure[7] was extended to prepare *S*-methyl- and *S*-isopropyl-L-cysteine. Since the L-cysteine purchased was in the anhydrous, free base form, only 2 equiv of sodium metal were added relative to the amino acid rather than the reported 4 equiv added to L-cysteine monohydrochloride monohydrate.

Scheme IV



Dimethylamino Acids (6a,c, 11). *S*-methyl- and *S*-isopropyl-L-cysteine, L-methionine, and D-penicillamine were subjected to hydrogenation in the presence of formaldehyde according to the literature procedure.[8] The crude *N,N*-dimethyl amino acids (including 11) were subjected to reduction without recrystallization.

Dimethylamino Alcohols 7a–c, 12. The reported procedure[4a,15] was modified and scaled down. This is illustrated for the preparation of (*R*)-2-(dimethylamino)-3-(methylthio)-1-propanol (**7a**): $LiAlH_4$ (5.7 g, 150 mmol) was suspended in 150 mL of freshly distilled THF at 0 °C. With stirring, *S*-methyl-*N,N*-dimethyl-L-cysteine (10.0 g, 61.4 mmol) was added in small portions over 20 min. The resulting slurry was stirred at 0 °C for 15 min and at room temperature for 30 min and then was refluxed for 4 h. Hydrolysis at 0 °C (with 7 mL of H_2O, 7 mL of 15% NaOH, and 25 mL of H_2O), filtration, and copious washing of the solids with ether (4 × 100 mL) gave 7.2 g of clear oil after drying and evaporation. Distillation gave material pure in the NMR (5.8 g, 39 mmol, 63% yield): bp 154 °C (2 torr); $[\alpha]^{21}_D$ +25.6° (1 dm, neat); ^1H NMR ($CDCl_3$) δ 3.93–3.23 (m, 2 H), 3.34 (s, 1 H), 3.05–2.59 (m, 2 H), 2.47–2.24 (m, 1 H), 2.34 (s, 6 H), 2.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 63.55, 59.84, 39.64, 29.26, 15.46: mass spectrum *m/e* 88 (100%), 118 (18.3%), 149 (2.8%, parent).

Anal. Calcd. for $C_6H_{15}NOS$: C, 48.28; H, 10.13; N, 9.38; S, 21.48. Found: C, 48.32; H, 10.22; N, 9.40; S, 21.48.

It was also found that L-cysteine could be taken through S-alkylation, reductive N-alkylation, and reduction in 50% overall yield without purification of intermediates by crystallization.

(*R*)-2-(Dimethylamino)-3-[(2-propyl)thio]-1-propanol (7b) was prepared in 50% yield from L-cysteine: bp (Kugelrohr) 140 °C (0.4 torr; ^1H NMR ($CDCl_3$) δ 3.82–3.22 (m, 2 H), 3.61 (s, 1 H), 3.10–2.40 (m, 4 H), 2.33 (s, 6 H), 1.24 (d, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 64.24, 60.07, 39.79, 34.91, 25.44, 22.70; mass spectrum, *m/e* 88 (100%), 146 (11.6%), 177 (0.8%, parent); $[\alpha]^{22}_D$ +23.5° (1 dm, neat). A satisfactory elementary analysis was not obtained although the ligand **15b** (see further) derived from this product did have a correct analysis.

(*S*)-2-(Dimethylamino)-4-(methylthio)-1-butanol (7c) was prepared in 60% yield from L-methionine: bp (Kugelrohr) 150 °C (2 torr); ^1H NMR ($CDCl_3$) δ 3.74–3.12 (m, 2 H), 3.33 (s, 1 H), 3.03–2.35 (m, 3 H), 2.39 (s, 6 H), 2.09 (s, 3 H), 1.92–1.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 63.28, 60.18, 39.71, 31.14, 23.98, 14.80; mass spectrum, *m/e* 61 (100%), 132 (19.6%), 163 (6.8%, parent); $[\alpha]^{20}_D$ +37.41° (*c* 1.16, CH_2Cl_2) [lit.[16] $[\alpha]^{20}_D$ +35.0° (*c* 1.1, CH_2Cl_2). The rotation reported here is of carefully distilled material.

A sample of **7c** (20 mg) and $Eu(hfc)_3$ was dissolved in $CDCl_3$ in an NMR tube. In the ^1H NMR spectrum the $N(CH_3)_2$ absorption was shifted 3.85 ppm downfield and the SCh_3 absorption 0.5 ppm downfield. In a separate experiment with *racemic* **7c** two $N(CH_3)_2$ absorptions separated by 0.22 ppm and two SCH_3

(11) (a) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547 and references cited therein. (b) Komiya, S.; Abe, Y.; Yamamoto, A.; Yamamoto, T. *Organometallics* **1983**, *2*, 1466 and references cited therein. (c) The results cited in ref 11b are especially pertinent since they deal with the thermal decomposition of cis nickel complexes (Tsou and Kochi have investigated the trans complexes). The thermal decomposition is accelerated by free ligands, which may add to form pentacoordinated intermediates from which decomposition occurs.

(12) The diorganonickels studied by Tsou and Kochi[11] are, however, uniformly trans substituted.

(13) For some evidence in support of this assertion, see: Hayashi, T.; Fukushima, M.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1980**, 79.

(14) Ireland, R. E.; Walba, D. M. *Org. Synth.* **1977**, *56*, 44.

(15) Vogl, O.; Pohm, M. *Monatsh. Chem.* **1952**, *83*, 541.

(16) Banfi, F.; Cinquini, M.; Colonna, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1841.

absorptions separated by 0.07 ppm were observed in the presence of Eu(hfc)$_3$. Addition of 5 mg of *rac*-**7c** to the optically pure material gave rise to new peaks in the expected ratio next to the $N(CH_3)_2$ and SCH_3 absorptions.

Anal. Calcd for $C_7H_{17}NOS$: C, 51.49; H, 10.50; N, 8.58; S, 19.64. Found: C, 51.41; H 10.44; N, 8.64; S, 19.65.

(*R*)-5,5-Dimethyl-4-(hydroxymethyl)-3-methylthiazolidine (12) was obtained in 68% yield from D-penicillamine: bp (Kugelrohr) 180 °C (2 torr); ^{1}H NMR ($CDCl_3$) δ 4.25 (d, J = 9 Hz, 1 H), 3.75 (d, J = 9 Hz, 1 H), 3.64 (d, J = 6.5 Hz, 2 H), 2.92 (s, 1 H), 2.67–2.39 (m, 1 H), 2.58 (s, 3 H), 1.50 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 78.36, 59.28, 54.94, 42.35, 31.27, 26.64; mass spectrum, m/e 130 (100%), 161 (2.9%, parent); $[\alpha]^{22}_D$ +58.7° (1 dm, neat).

The elementary analysis was unsatisfactory.

(*S*)-2-(Dimethylamino)-3-methyl-1-butanol was prepared by the literature procedure[4a] in 40% yield from L-valine: bp (Kugelrohr) 90 °C (2 torr); $[\alpha]^{21}_D$ −3.59° (1 dm, neat) [lit.[4a] $[\alpha]^{25}_D$ −0.368° (neat, 0.1 dm)].

(*R*)-2-(Dimethylamino)-3-methyl-3-(methylthio)-1-butanol (9) had to be prepared by a more circuitous route. S-Alkylation by the procedure used for preparation of **5a,b**[7] was not possible because the NaI, formed as a reaction byproduct, could not be adequately separated from the organic product. This NaI poisons the Pd catalyst required for the subsequently alkylation step. For this reason the following modification was developed.

D-Penicillamine (3.0 g, 20 mmol) was slurried in absolute C_2H_5OH (40 mL). To this was added, with stirring, Na metal (0.92 g, 40 mmol) in three portions. After the last piece of metal had disappeared, CH_3I (1.37 mL, 22 mmol) was added via graduated pipet. This caused an extremely fast reaction to occur, in which the disodium salt of D-penicillamine (insoluble in C_2H_5OH) reacted and dissolved almost instantaneously. The mixture was stirred for 5 min and then evaporated. The white solid was crushed to a powder in the same flask, treated with 50 mL of freshly-distilled THF, and cooled to 0 °C. $LiAlH_4$ (3.0 g, 80 mmol) was added very carefully with stirring. The resulting slurry was stirred at 0 °C for 15 min and at room temperature for 0.5 h and refluxed for 4 h. After hydrolysis at 0 °C with 25 mL of damp $(C_2H_5)_2O$, 5 mL of H_2O, 5 mL of 15% NaOH, and 10 mL of H_2O, the mixture was filtered, and the solids were rinsed copiously (6 × 50 mL) with ether. After drying over Na_2SO_4 and evaporation there was obtained 3.06 g of oil, shown to be the *S*-methylamino alcohol (90% pure). This was cooled to 0 °C and treated with 37% aqueous formaldehyde (4.5 mL, 55 mmol). The white mixture was stirred for 10 min, then treated with formic acid (4.2 mL, 110 mmol) dropwise, and then heated to 75–80 °C for 15 h, after which time no more evolution of CO_2 had been noted for 1 h. The mixture was cooled to 0 °C, treated with 50 mL of 10% HCl, and extracted with 25 mL of CH_2Cl_2. The aqueous phase was then adjusted to pH 10 and extracted with 3 × 50 mL of CH_2Cl_2. The extracts were combined, dried over Na_2SO_4, and evaporated. There was obtained 3.1 g of crude material. Kugelrohr distillation gave 2.54 g (14.4 mmol, 72% yield) of product: by 150 °C (0.7 torr); ^{1}H NMR ($CDCl_3$) δ 4.08–3.51 (m, 2 H), 2.92–2.35 (m, 1 H), 2.82 (s, 1 H), 2.60 (s, 6 H), 2.05 (s, 3 H), 1.38 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 70.94, 58.01, 47.89, 42.48, 26.64, 25.08, 10.53; mass spectrum, m/e 88 (100%), 99 (11%), 130 (61%), 146 (2.4%) (the parent peak was not observed owing to the ready loss of CH_2OH); $[\alpha]^{22}_D$−6.4° (1 dm, neat). Esterification with (*R*)-3,3,3-tris(fluoromethyl)-2-methoxy-2-phenylpropionyl chloride gave a product that revealed in the ^{19}F NMR two absorptions at −71.44 and −71.51 ppm (relative to $CFCl_3$) in the ratio 10:1. The methoxy peaks were not split in the ^{1}H NMR. The enantiomeric excess is 81%; $[\alpha]_D$ for the optically pure material is calculated to be −7.9°.

Anal. Calcd for $C_8H_{19}NS$: C, 54.19; H, 10.80; N, 7.90; S, 18.08. Found: C, 52.86; H, 10.41; N, 7.86; S, 17.54. The analysis could not be improved.

Preparation of Diphenylphosphine Derivatives 15a–e. A representative synthesis is given, namely, for (*S*)-2-(dimethylamino)-1-(diphenylphosphino)-3-(methylthio)propane (**15a**, (*S*)-methylcysphos). This is substantially modified relative to the literature procedure.[4a]

A dry, 100-mL, two-necked flask was charged with a stirring egg, proton sponge (2.34 g, 11 mmol), and 30 mL of freshly distilled THF. This was swept with nitrogen and kept under positive nitrogen pressure thereafter. The solution was cooled to 0 °C, and methanesulfonyl chloride was added (0.88 mL, 11 mmol) in one portion via graduated pipet. After 5 min the alcohol **7a** (1.49 g, 10 mmol) was added neat, dropwise over 10 min. The resulting mixture was allowed to stir for 1 h at 0 °C and then warmed out of the cooling bath for 20 min. The mixture was cooled again to 0 °C and treated with a deep red mixture of $(C_6H_5)PH$ (1.78 mL, 10 mmol) and $KOC(CH_3)_3$ (2.8 g, 25 mmol) in 45 mL of freshly distilled THF, in one portion. The deep red color faded immediately to give a thick, orange-yellow mixture, which was allowed to warm and stir at room temperature for 2 h. The mixture was then filtered to remove as much proton sponge as possible, evaporated, taken up in 50 mL of 15% NaOH, and extracted with 2 × 50 mL of C_6H_6. The C_6H_6 fractions were combined, washed with brine, dried over Na_2SO_4, and evaporated to give 5 g of crude oil. This showed a phosphine/alcohol ratio of 1.5:1. This was subjected to Kugelrohr distillation at 2 torr (250 °C) and then at 0.001 torr (proton sponge, excess C_6H_5PH, and starting alcohol distilled at 2 torr). There was obtained 0.80 g (2.52 mmol, 25% yield) of **15a** as a colorless oil: bp 200 °C (2 torr); ^{1}H NMR ($CDCl_3$) δ 7.50–7.35 (m, 4 H), 7.30–7.24 (m, 6 H), 2.72–2.47 (m, 3 H), 2.35–2.08 (m, 2 H), 2.16 (s, 6 H), 1.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.77 (d, J = 7.3 Hz), 138.22 (d, J = 7.3 Hz), 132.42 (d, J = 19.2 Hz), 128.02 (s), 127.74 (s), 60.07 (d, J = 14.3 Hz), 39.50 (s), 35.18 (d, J = 7.5 Hz), 28.20 (d, J = 13.5 Hz), 15.50 (s); mass spectrum, m/e 185 (64.3%), 256 (100%), 302 (18.4%) (the parent peak could not be observed owing to the loss of methyl); $[\alpha]^{21}_D$ +9.12° (*c* 1.25, $CHCl_3$).[17]

Anal. Calcd for $C_{18}H_{24}NSP$: C, 68.11; H, 7.62; N, 4.41; S, 10.10; P, 9.76. Found: C, 68.13; H, 7.52; N, 4.37; S, 9.60; P, 10.03.

In a similar manner **(*S*)-2-(dimethylamino)-1-(diphenylphosphino)-3-[(2-propyl)thio]propane (15b, (*S*)-*S*-isopropylcysphos)** was obtained in 29% yield: bp (Kugelrohr) 220–250 °C (10^{-3} torr); ^{1}H NMR ($CDCl_3$) δ 7.70–7.20 (m, 10 H), 3.11–2.00 (m, 6 H), 2.19 (s, 6 H), 1.21 (d, J = 6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.9 (d, J = 4.9 Hz), 138.4 (d, J = 4.9 Hz), 132.7 (d, J = 19.0 Hz), 128.2 (s), 128.0 (s), 61.0 (d, J = 14.8 Hz), 39.8 (s), 35.0 (s), 31.8 (d, J = 7.3 Hz), 28.4 (d, J = 13.6 Hz), 23.2 (s); mass spectrum, m/e 146 (41.3%), 185 (79.1%), 256 (88.7%), 302 (100%) (the parent peak could not be observed owing to the loss of isopropyl); $[\alpha]^{21}_D$ −5.44° (*c* 1.08, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{28}NPS$: C, 69.53; H, 8.17; N, 4.05; P, 8.96; S, 9.28. Found: C, 69.21; H, 8.15; N, 3.97; P, 9.17; S, 9.18.

(*S*)-2-(Dimethylamino)-1-(diphenylphosphino)-4-(methylthio)butane (15c, (*S*)-methphos) was obtained in 28% yield: bp (Kugelrohr), 210–230 °C (10^{-3} torr); ^{1}H NMR ($CDCl_3$) δ 7.54–7.30 (m, 4 H), 7.30–7.22 (m, 6 H), 2.62–2.40 (m, 4 H), 2.38–2.21 (m, 1 H), 2.11 (s, 6 H), 2.00 (s, 3 H), 1.92–1.60 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 139.0 (t, J = 13.7 Hz), 133.0 (d, J = 13.2 Hz), 132.3 (d, J = 12.6 Hz), 128.4 (d, J = 5.2 Hz), 128.0 (d, J = 3.1 Hz), 59.8 (d, J = 15 Hz), 39.6 (s), 31.40 (s), 30.8 (d, J = 6.3 Hz), 27.4 (d, J = 15.2 Hz), 15.2 (s); mass spectrum, m/e 132 (100%), 256 (4.3%), 316 (16.7%) (a methyl group fragments from the parent molecular ion); $[\alpha]^{21}_D$ − 68.4 ° (*c* 1.00, $CHCl_3$).

Anal. Calcd for $C_{19}H_{26}NPS$: C, 68.85; H, 7.91; N, 4.23; P, 9.34; S, 9.67. Found: C, 68.92; H, 7.98; N, 4.34; P, 9.61; S, 9.55.

(*R*)-2-(Dimethylamino)-1-(diphenylphosphino)-3-methyl-3-(methylthio)butane (15d, (*R*)-*S*-methylpenphos) was prepared in 29% yield: bp (Kugelrohr) 230–250 °C (10^{-3} torr); ^{1}H NMR ($CDCl_3$) δ 7.80–7.20 (m, 10 H), 3.2–2.0 (m, 3 H), 2.50 (s, 6 H), 1.78 (s, 3 H), 1.30 (s, 3 H), 1.23 (s, 3 H), ^{13}C NMR ($CDCl_3$) δ 10.6 (s, $(CH_3)_2C$), 24.4 (s, SCH_3), 26.2 (d, $J_{P-^{13}C}$ not measured, CH_2P), 42.9 (s, $(CH_3)_2N$), 50.8 (s, $C(CH_3)_2$), 66.7 (d, $J_{P-^{13}C}$ not measured, $CHN(CH_3)_2$), 131.8 (d, $J_{P-^{13}C}$ not measured, aryl), 133.7 (d, $J_{P-^{13}C}$ not measured, aryl), 137.8 (d, $J_{P-^{13}C}$ not measured, quat aryl), 140.5 (d, $J_{P-^{13}C}$ not measured, quat aryl) (the effects of

(17) We have subsequently found (Vriesema, B. K., unpublished results) that proton sponge can usually be replaced by triethylamine (5% excess). During workup the unconsumed triethylamine is removed readily by rotary evaporation. Further purification can then be accomplished by column chromatography over closely packed Al_2O_3 rather than by Kugelrohr distillation (needed to separate from excess proton sponge). The yield of **15c** prepared by this method was ±80%, the rotation was identical with that described in the Experimental Section.

diastereotopicity are apparent in the aryl portion. Carbon assignments were made from the ^1H-coupled (^{31}P-decoupled) spectrum, which revealed, in order of increasing ppm, multiplicities q, q, t, q, s, d, d, d, d, s, s, the latter two singlets arising from the two diastereotopic quaternary aryl carbons at 137.8 and 140.5 ppm); mass spectrum, *m/e* 100 (100%), 185 (22.5%), 256 (47.0%), 299 (3.1%) (the fragment CH_3S is lost); $[\alpha]^{21}_D$ −133.2° (*c*, 1.08, $CHCl_3$) (assuming an ee of 81% the theoretical rotation is −164.4°).

Owing to an administrative mistake, the sample submitted for analysis was lost. The material has not been resynthesized nor was there any material for an exact mass spectral determination.

(*R*)-5,5-Dimethyl-4-[(diphenylphosphino)methyl]-1,3-thiazolidine (15e, (*R*)-cyclopenphos) was obtained in 20% yield: bp (Kugelrohr) 250 °C (10^{-3} torr); ^1H NMR ($CDCl_3$) δ 7.70–7.12 (m, 10 H), 4.07 (d, *J* = 8 Hz, 1 H), 3.78 (d, *J* = 8 Hz, 1 H), 2.53 (s, 3 H), 2.60–2.08 (m, 3 H), 1.45 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 133.2 (d, *J* = 19.9 Hz), 132.2 (d, *J* = 18.6 Hz), 128.9 (s), 128.4 (s), 128.3 (s), 73.3 (*J* = 12.4 Hz), 59.2 (s), 56.4 (d, *J* = 4.9 Hz), 39.7 (d, *J* = 6.1 Hz), 30.15 (d, *J* = 1.8 Hz), 27.9 (s), 27.4 (d, *J* = 15.8 Hz); mass spectrum, *m/e* 144 (100%), 328 (7.3%), 329 (2.5%, parent), 330 (6.1%), theoretical *m/e* 329 for $C_{19}H_{24}NSP$. The optical rotation was not measured and a satisfactory elemental analysis could not be obtained.

(*S*)-2-(Dimethylamino)-1-(diphenylphosphino)-3-methylbutane (valphos) was prepared in 25% yield using the described procedure.[17]

Cross Coupling Reactions. The synthesis of the Grignard reagent of 1-phenyl-1-chloroethane was carried out by two different procedures.

Method A: In $(C_2H_5)_2O$ (80 mL) 1-phenyl-1-chloroethane (10.5 g, 75 mmol) was dissolved. Freshly activated Mg turnings (2.02 g, 83 mmol) were added, and the reaction was started with a crystal of I_2 and held at 0–5° until cessation of reaction. The entire Grignard solution was decanted from the unreacted turnings into an addition funnel. This was added to a suspension of $NiCl_2$ (7 mg, 0.13 mmol), ligand (0.13 mmol), and vinyl bromide (2.68 g, 25 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 room temperature over a period of 14 h. The reaction mixture was hydrolyzed at 0 °C with 10% HCl solution (30 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 10% HCl solution (30 mL). 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.

Method B differs in the preparation of the Grignard reagent: For both 1-phenyl-1-chloroethane and 2-chlorooctane the Grignard reagents were prepared on a 500-mmol scale as described above but in a large Schlenk vessel under N_2 dried by passage over P_2O_5/CaO and Cu turnings. 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 the case of the Grignard reagent of 1-phenyl-1-chloroethane, prepared by method A or B, an aliquot was removed, hydrolyzed with 10% HCl solution, and then back-titrated with base. In some cases the hydrocarbon formed on hydrolysis was analyzed by ^1H NMR spectroscopy to determine the ratio of ethylbenzene to the (diastereomeric) 2,3-diphenylbutanes.

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Registry No. L-**3**, 52-90-4; L-**4**, 63-68-3; (*R*)-**7a**, 97071-92-6; (*R*)-**7b**, 97071-93-7; (*S*)-**7c**, 79546-64-8; (*R*)-**9**, 97072-01-0; (*R*)-**10**, 97071-94-8; (*R*)-**12**, 97071-95-9; (*S*)-**15a**, 97071-96-0; (*S*)-**15b**, 97071-97-1; (*S*)-**15c**, 97071-98-2; (*R*)-**15d**, 97071-99-3; (*R*)-**15e**, 97072-00-9; (*S*)-**15f**, 74492-09-4; **19**, 593-60-2; (*S*)-**20a**, 58717-85-4; (*R*)-**20a**, 36617-88-6; (*R*)-**20b**, 54541-44-5; (*S*)-**20b**, 54541-45-6; HCHO, 50-00-0; CH_3SO_2Cl, 124-63-0; $(C_6H_5)_2Ph$, 829-85-6; *S*-methyl-*N*,*N*-dimethyl-L-cysteine, 70706-62-6; D-penicillamine, 52-67-5; (*S*)-2-(dimethylamino)-3-methyl-1-butanol, 64584-88-9; (*R*)-3,3,3-tris(fluoromethyl)-2-methoxy-2-phenylpropionyl chloride, 39637-99-5; (*R*)-2-(dimethylamino)-3-methyl-3-(methylthio)-1-butyl (*S*)-3,3,3-tris(fluoromethyl)-2-methoxy-2-phenylpropionate, 97072-02-1; (±)-1-phenyl-1-chloroethane, 38661-82-4; (±)-2-chlorooctane, 51261-14-4.

Formation and Uses of the Dianion Formally Produced by Conjugate Addition of Bis(phenylthio)methyl Dianion to Cyclohex-2-en-1-one. Configurations and Conformations of the Products of Conjugate Addition of Tris(phenylthio)methyllithium to Carvone

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When the enolate anion formed by the addition of tris(phenylthio)methyllithium to 2-cyclohexen-1-one is treated at −50 °C with *sec*-butyllithium, the enolate thioacetal dianion **3** is generated. The latter forms useful compounds by the attack of electrophiles (protons, aldehydes, and methyl iodide) at the thioacetal carbanionic site, but alkylating agents bulkier than methyl iodide are unreactive toward this site; the behavior toward some of these is chronicled. Methylation of the protonation product **14** of **3** apparently occurs at a sulfur atom, yielding the norcaranone **15**. A similar dianion is produced when (−)-carvone is the substrate; in this case, the conjugate addition occurs from the side opposite the isopropenyl substituent, and the structures and conformations of the original adduct have been determined by 300-MHz NMR spectroscopy.

The readily prepared tris(phenylthio)methyllithium (**1**) undergoes high-yield conjugate addition to cyclohex-2-en-1-one.[1,2] We have found that the proximate product, the enolate anion **2**, undergoes clean sulfur–lithium exchange at −45 °C in the presence of *sec*-butyllithium to produce the dianion **3** (Scheme I), the formal conjugate adduct of the unknown bis(phenylthio)methyl dianion to

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