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5-Aza-Semicorrins: A New Class of Bidentate Nitrogen Ligands for Enantioselective Catalysis

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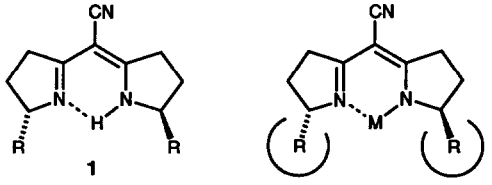
Key Words: enantioselective catalysis; chiral nitrogen ligands; cyclopropanation; allylic alkylation; Pd catalysts.

Abstract: *C_2-symmetric 5-aza-semicorrins are readily prepared in enantiomerically pure form starting from pyroglutamic acid. Methylation at N(5) leads to neutral bidentate nitrogen ligands. Copper(I) and palladium(II) complexes of these ligands have proved to be efficient enantioselective catalysts for the cyclopropanation of olefins and for allylic nucleophilic substitutions.*

The stereochemical course of a metal-catalyzed reaction can be effectively controlled by an appropriate organic ligand attached to the metal center. The design and synthesis of suitable ligands for this purpose presents a challenging task for organic chemists. In the past two decades, a number of chiral ligands have been found that allow a metal-catalyzed process to be directed in such a way that one of two enantiomeric products is formed with high preference over the other.[1]



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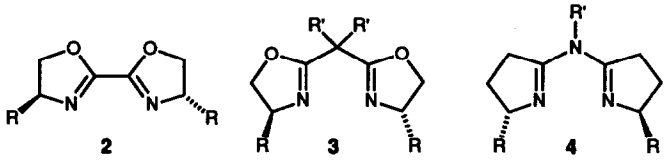
We have developed an efficient synthesis of chiral C_2-symmetric semicorrins **1**, starting from pyroglutamic acid.[2,3] These compounds possess a number of features which make them attractive ligands for enantioselective control of metal-catalyzed reactions. Both enantiomers are readily prepared in optically pure form. The synthesis is flexible and allows for a wide range of structural variations. In a metal complex, the two substituents at the stereogenic centers are held in close proximity to the metal by the rigid ligand scaffold and, therefore, are expected to have a strong influence on a reaction taking place in the coordination sphere of the complex. The remarkable enantioselectivities induced by semicorrins in the copper-catalyzed cyclopropanation of olefins[2a,4] and in the cobalt-catalyzed conjugate reduction of α,β-unsaturated carboxylic esters and amides[5] demonstrate that the stereochemical course of a metal-catalyzed process can be effectively controlled by these ligands.[6,7]

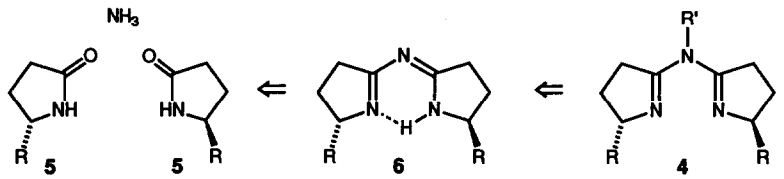


Because of the electron-rich vinylogous amidine system and the negative charge, semicorrin ligands **1** are expected to act as σ- and π-electron-donors on a coordinated metal ion. However, for certain applications structurally analogous neutral ligands, which are weaker electron-donors or even π-acceptors, would be preferable. Possible candidates for ligands of this type are the C_2-symmetric oxazoline derivatives **2** and **3** which have been recently reported by several research groups including ours,[8,9] and the 5-aza-semicorrins **4**. Bioxazolines **2** have been successfully employed as ligands for enantioselective rhodium-catalyzed hydrosilylations,[8e] iridium-catalyzed transfer hydrogenations of ketones[9], and for palladium-catalyzed allylic alkylations.[9] Copper(I) triflate complexes of methylene-bis(oxazolines) **3** (R'=methyl) were found to be highly efficient enantioselective catalysts for the cyclopropanation of olefins,[8b] whereas corresponding iron(III) complexes gave promising results in a Lewis-acid-catalyzed Diels-Alder reaction.[8c] Herein, we describe the synthesis of enantiomerically pure 5-aza-semicorrins **4** and their application as ligands for enantioselective copper-catalyzed cyclopropanations and palladium-catalyzed allylic alkylations.

SYNTHESIS OF 5-AZA-SEMICORRINS

Chiral C_2-symmetric 5-aza-semicorrins **4** are readily assembled from appropriate butyrolactam derivatives **5** (Scheme 1). As for the semicorrins **1**[2], pyroglutamic acid **5** (R = COOH) serves as a versatile, inexpensive precursor. Both D- and L-pyroglutamic acid as well as the hydroxymethyl derivative **5** (R = CH_2OH), which can be prepared by selective reduction of methyl pyroglutamate, are commercially available.

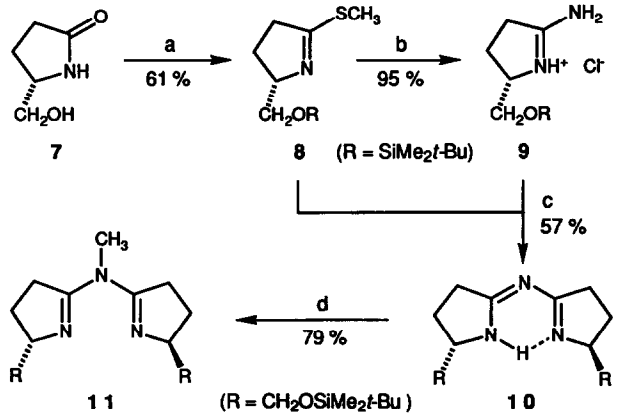
Scheme 1



The synthesis of the bis(silyloxymethyl)-substituted ligand **11** is summarized in Scheme 2. Silylation of the alcohol **7**, conversion to the corresponding thiolactam using Lawesson's reagent,[10] and subsequent *S*-methylation with methyl iodide led to the thioimidate **8** in good overall yield. Treatment with equimolar amounts of ammonium chloride in refluxing methanol afforded the crystalline amidinium chloride **9** in essentially quantitative yield. Condensation of the thioimidate **8** with the free amidine, generated by deprotonation of the hydrochloride **9** with 0.9 molar equivalents of butyllithium, led to the aza-semicorrin **10**.[11] The reaction was carried out without solvent in an evacuated ampule at 70 °C. The presence of 10-20 % of protonated amidine was found to be crucial; when the hydrochloride **9** was neutralized with ≥1.0 molar equivalents of base, only

traces of the desired product **10** were formed. Deprotonation of **9** by extraction with aqueous base is also possible. However, the use of butyllithium gave higher yields. As expected, alkylation of ligand **10** with methyl iodide occurs exclusively at the aza bridge rather than at the endocyclic nitrogen atoms which are protected by the intramolecular hydrogen bond. The resulting crystalline hydroiodide of **11** was isolated in 79 % yield. The free ligand **11**, which was easily obtained by extraction of a methylene chloride solution of the hydroiodide with aqueous sodium carbonate, could not be crystallized. The overall yield of the 5-aza-semicorrin **11**, starting from **7**, was in the range of 20-30 %.

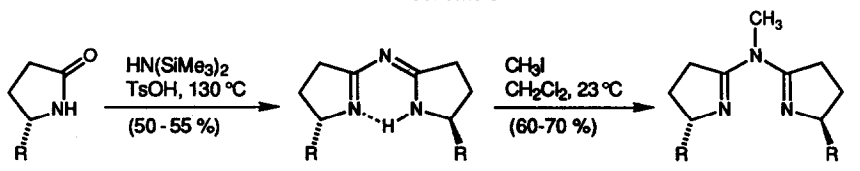
Scheme 2



(a) Me_2t-BuSiCl, imidazole, 40 °C; Lawesson's reagent[10], THF, 23 °C; MeI, CH_2Cl_2, 23 °C; $NaHCO_3$, CH_2Cl_2, H_2O. (b) NH_4Cl, MeOH, refl. (c) **9** (1 equiv.), BuLi (0.9 equiv), THF, 0-23 °C; **8** (1 equiv.), 72 °C. (d) MeI, 23 °C; $NaHCO_3$, CH_2Cl_2, H_2O.

A much shorter route to ligands of this type is based on the method developed by Vorbrüggen for the conversion of amides and lactams to amidines.[12] Treatment of the lactam **12**, prepared from methyl pyroglutamate **5** (R=CO_2Me) by Grignard reaction, with an excess of bis(trimethylsilyl)amine and catalytic amounts of *p*-toluenesulfonic acid at 130 °C led directly to the 5-aza-semicorrin **13** in 50-55 % yield (Scheme 3). Alkylation with methyl iodide, as described above, afforded the *N*-methyl derivative **14**. This route is particularly suited for the synthesis of the silylated tertiary diols **13** and **14**. Reaction of the primary alcohol **7** or the silylated derivative **5** (R = CH_2OSiMe_2t-Bu) with bis(trimethylsilyl)amine gave distinctly lower and less reproducible yields (10-30 %) of the corresponding aza-semicorrins.

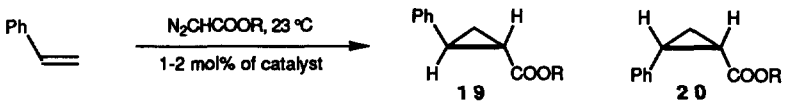
Scheme 3



ENANTIOSELECTIVE CYCLOPROPANATION

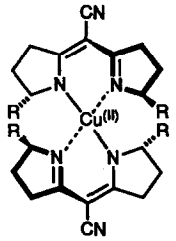
The first enantioselective catalyst for the cyclopropanation of olefins with diazo compounds was found by Nozaki and coworkers more than 20 years ago.[13] Although the selectivity of their original (salicylaldiminato)-copper catalyst was low, extensive modification of the catalyst structure by Aratani and his group eventually led to highly selective catalysts for this class of reactions.[14] Another group of efficient enantioselective catalysts, which are particularly well suited for the cyclopropanation of terminal olefins, are (semicorrinato)copper compounds, such as **15**,[2a,4,6] and the structurally related bis(oxazoline) complexes **16**.[8a,9] Recently, Evans *et al.* reported an even more selective cyclopropanation catalyst prepared from copper(I) triflate and the neutral bis(oxazoline) ligand **17**.[8b] In view of these results, we decided to study the analogous catalysts derived from neutral 5-aza-semicorrin ligands and copper(I) triflate.

Table 1. Enantioselective Cyclopropanation of Styrene

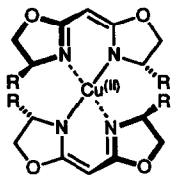


Catalyst	Diazoacetate R	Solvent	% Yield 19+20	trans/cis Ratio 19 : 20	% ee 19	% ee 20	Configuration[a] 19	Configuration[a] 20
11/Cu(I)OTf	Ethyl	$CHCl_3$	40	75 : 25	66	43	1*S*,2*S*	1*S*,2*R*
14/Cu(I)OTf	Ethyl	$CHCl_3$	80	75 : 25	94	68	1*S*,2*S*	1*S*,2*R*
18/Cu(I)OTf	Ethyl	$CHCl_3$	45	77 : 23	95	90	1*S*,2*S*	1*S*,2*R*
14/Cu(I)OTf	*tert*-Butyl	$CHCl_3$	87	86 : 14	96	90	1*S*,2*S*	1*S*,2*R*
18/Cu(I)OTf	*tert*-Butyl	$ClCH_2CH_2Cl$	75	81 : 19	94	95	1*S*,2*S*	1*S*,2*R*
14/Cu(I)OTf	*d*-Menthyl[f]	$ClCH_2CH_2Cl$	89	84 : 16	98	99	1*S*,2*S*	1*S*,2*R*
18/Cu(I)OTf	*d*-Menthyl[f]	$ClCH_2CH_2Cl$	75	84 : 16	98	99	1*S*,2*S*	1*S*,2*R*
17/Cu(I)OTf[b]	Ethyl	$CHCl_3$	77	73 : 27	99	97	1*R*,2*R*	1*R*,2*S*
17/Cu(I)OTf[b]	*tert*-Butyl	$CHCl_3$	75	81 : 19	96	93	1*R*,2*R*	1*R*,2*S*
15[c]	Ethyl	$ClCH_2CH_2Cl$	65	73 : 27	92	79	1*S*,2*S*	1*S*,2*R*
15[d]	*d*-Menthyl[f]	$ClCH_2CH_2Cl$	70	82 : 18	97	95	1*S*,2*S*	1*S*,2*R*
16[e]	Ethyl	$ClCH_2CH_2Cl$	80	75 : 25	90	77	1*R*,2*R*	1*R*,2*S*
16[e]	*l*-Menthyl[g]	$ClCH_2CH_2Cl$	72	86 : 14	98	96	1*R*,2*R*	1*R*,2*S*

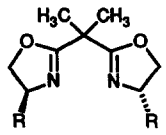
(a) Assignments according to ref. 4. (b) Results taken from ref. 8b. (c) 2 mol% of catalyst, activation with phenylhydrazine.[24] (d) Results taken from ref. 4. (e) Results taken from ref. 8a; we have obtained similarly high selectivities using catalyst **16**.[9,25] (f) (1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl, from (+)-menthol. (g) (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl, from (–)-menthol.



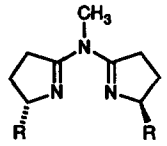
15 (R = CMe_2OH)



16 (R = CMe_3)



17 (R = CMe_3)



14 (R = CMe_2OSiMe_3)
18 (R = CMe_2OSiMe_2t-Bu)

Our findings and some representative results obtained with other copper complexes are summarized in Table 1. The catalysts were prepared *in situ* from copper(I) triflate and a slight excess of the corresponding aza-semicorrin, following the procedure of Evans *et al.*[8b] The copper(I) complexes of **14** and **18** proved to be efficient cyclopropanation catalysts. In the presence of 1-2 mol% of these catalysts, ethyl, *tert*-butyl, and menthyl diazoacetate reacted with styrene to afford enantiomeric excesses exceeding 90% ee for the trans product **19**. Analogous ligands with less bulky substituents at the stereogenic centers, such as **11**, gave distinctly lower enantioselectivities. Taking the enantiomeric purity of the trans product **19** as a measure, the selectivities of the aza-semicorrin catalysts derived from **14** and **18** range between those obtained with the Evans catalyst Cu(I)OTf/**17** and the copper complexes **15** and **16**.

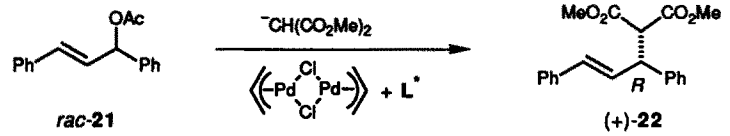
PALLADIUM-CATALYZED ALLYLIC ALKYLATION

Palladium-based reagents and catalysts have become indispensable tools for organic synthesis. A particularly versatile, widely used class of palladium-catalyzed reactions are nucleophilic allylic substitutions[15] and the search for efficient enantioselective catalysts for this type of transformations is an obvious goal of current research in this area. During the last years, a number of chiral palladium phosphine complexes have been found which catalyze the conversion of achiral or racemic allylic substrates to optically active substitution products.[16] Striking examples are the ferrocenylphosphine palladium catalysts developed by Hayashi[16c] which were shown to induce excellent enantioselectivities of ≥90 %ee in certain reactions of allylic acetates with stabilized carbanions and amines. More recently, similarly high enantiomeric excesses have also been obtained using other types of chiral phosphine ligands.[16e]

Palladium complexes with nitrogen ligands, on the other hand, have received much less attention.[17] We have found that palladium(0) or (allyl)palladium(II) complexes of bioxazolines **2** can be used as enantioselective catalysts for allylic alkylations.[9] In the reaction shown in Table 2, we observed enantiomeric excesses of up to 77 % using an (allyl)palladium catalyst prepared from the dibenzyl-substituted bioxazoline **23**. The same levels of enantioselectivity have been recently reported by Togni for palladium-sparteine complexes as catalysts.[17b] Encouraged by the results obtained with bioxazolines, we have extended our studies to structurally related methylene-bis(oxazolines) and 5-aza-semicorrins.

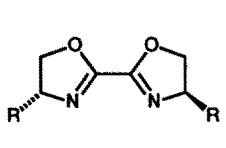
The first experiments were carried out using the sodium salt of dimethyl malonate as a nucleophile. Surprisingly, the bioxazoline **23** and the corresponding methylene-bis(oxazoline) **24** gave essentially identical results despite their potentially different coordination geometries (five- *vs.* six-membered chelate ring) and different electronic properties (**23** is a better π-acceptor than **24**). In THF, the reaction is rather slow. The use

Table 2. Enantioselective Allylic Alkylation Catalyzed by Palladium Complexes with Chiral Nitrogen Ligands

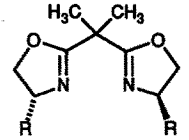


Entry	Ligand	Nucleophile	Solvent	Temp. °C	Time h	Yield[a] % of 22	Enantioselectivity %ee[b] of (+)-22[c]
1	**23**[d]	$NaCH(CO_2Me)_2$	THF	50	88	86	77
2	**24**[d]	$NaCH(CO_2Me)_2$	THF	50	91	85	76
3	**24**[d]	$CH_2(CO_2Me)_2$/BSA[f]	THF	50	94	95	73
4	**24**[d]	$CH_2(CO_2Me)_2$/BSA[f]	THF/Et_2O (1:1)	23	92	99	84
5	**24**[d]	$CH_2(CO_2Me)_2$/BSA[f]	CH_2Cl_2	23	68	97	88
6	**23**[d]	$CH_2(CO_2Me)_2$/BSA[f]	CH_2Cl_2/THF (9:1)	23	66	0	–
7	**11**[d]	$CH_2(CO_2Me)_2$/BSA[f]	CH_2Cl_2	23	24	99	95
8	**11**[d]	$CH_2(CO_2Me)_2$/BSA[f]	CH_2Cl_2	4	72	99	95
9	**11**[d]	$CH_2(CO_2Me)_2$/BSA[f]	CH_2Cl_2	-14	146	32	95
10	**11**[e]	$CH_2(CO_2Me)_2$/BSA[f]	CH_2Cl_2	23	118	97	95

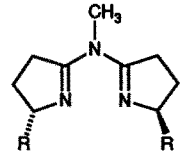
(a) Yield of analytically pure product after column chromatography. (b) Determined by ^{1}H-NMR spectroscopy in the presence of Eu(hfc)$_3$. (c) The (*R*)-configuration of (+)-22 was assigned according to ref. 16c. (d) 2.5 mol% of ligand, [Pd] / [ligand] (1:1.25), concentration of 21 ca. 0.2 M. (e) 1.25 mol% of ligand, [Pd] / [ligand] (1:1.25), concentration of 21 ca. 0.2 M. (f) 3 equiv. of dimethyl malonate, 3 equiv. of BSA (*N,O*-bis[trimethylsilyl]acetamide), 2 mol% of KOAc.



23 (R = CH_2Ph)



24 (R = CH_2Ph)



11 (R = CH_2OSiMe_2t-Bu)

of more polar solvents, such as DMSO, led to higher rates but the resulting enantioselectivities were distinctly lower. Apolar solvents, such as dichloromethane or diethyl ether, proved to be unsuitable because of insufficient solubility of sodium dimethyl malonate. However, using a mixture of dimethyl malonate and *N,O*-bis-(trimethylsilyl)actamide (BSA), as described by Trost[18], and the palladium catalyst derived from **24**, the reaction could be carried out in apolar solvents under mild conditions. The catalytic process was initiated by addition of a catalytic amount of potassium acetate. Under these conditions, the allylic acetate **21** was smoothly converted to the desired product **22** in essentially quantitative yield. In dichloromethane, the reaction was sufficiently fast even at 4 °C. The enantioselectivity in different solvents increased in the order THF < dioxane ≤ DME < benzene ≤ 1,2-dichloroethane ≤ dichloromethane. Interestingly, the palladium complex prepared from

the bioxazoline **23** proved to be unreactive under these conditions (Entry 6). The most selective and also most reactive catalyst was the palladium complex of the aza-semicorrin **11**. In a series of experiments using 1-2 mol% of catalyst, we obtained enantiomeric excesses of 95±0.5 % (Entries 7-10). This exceeds the enantioselectivities previously observed in this reaction with other catalysts.[16,17b] We are currently extending our studies to other nucleophiles and substrates in order to evaluate the scope and limitations of this new catalyst system.

CONCLUSION

The 5-aza-semicorrins **4**, which we designed as neutral counterparts of anionic semicorrin ligands, have proved to be effective ligands for enantioselective control in copper-catalyzed cyclopropanations and palladium-catalyzed allylic alkylations. The syntheses developed for these ligands are straightforward and flexible, and give access to a wide range of differently substituted derivatives. This allows the ligand structure to be adjusted to the specific requirements of a given application. Although the level of enantioselection primarily depends on the particular choice of the substituents at the stereogenic centers, it may be of interest as well to alter the substituent at the aza bridge in order to change the electronic properties or the solubility of the ligand. Furthermore, it should also be possible to attach the ligand to a polymer *via* the central nitrogen atom, in order to simplify catalyst recovery. In summary, proper selection of the substituents at the stereogenic centers and at the aza bridge should allow the development of tailor-made ligands for many different types of metal-catalyzed reactions.

Acknowledgements. We thank Prof. Vorbrüggen for a most fruitful discussion which formed the basis of the aza-semicorrin synthesis summarized in Scheme 3. Financial support by the Swiss National Science Foundation and F. Hoffmann-La Roche AG, Basel, is gratefully acknowledged.

EXPERIMENTAL

General. *Chemicals:* DMF, ethanol, and methanol: *Fluka puriss.*; Et_2O and THF: *Fluka purum*, distilled from Na/benzophenone; chloroform, 1,2-dichloroethane, dichloromethane: *Fluka puriss.*, filtered through basic alumina (*ICN Biomedicals*, Super I); (*S*)-5-(hydroxymethyl)-2-pyrrolidinone **7**: *Fluka puriss.*; (*tert*-butyl)-dimethylchlorosilane and (*tert*-butyl)dimethylsilyl triflate: *Fluka purum*; hexamethyldisilazane: *Fluka puriss.*; 2,6-lutidine: *Fluka purum*; toluene-4-sulfonic acid monohydrate: *Fluka puriss.*; dimethyl malonate and *N,O*-bis-(trimethylsilyl)acetamide: *Fluka purum*; Lawesson's reagent: *Fluka purum*; styrene: *Fluka purum*, freshly distilled; ethyl diazoacetate: *Fluka purum*; imidazole: *Fluka puriss.*; copper(I) trifluoromethanesulfonate benzene complex $[Cu(OTf)(C_6H_6)_{0.5}]$: *Fluka pract.* Unless otherwise stated, reactions were carried out under N_2 using dried glassware. Flash column chromatography: silica gel C 560, 0.035-0.070 mm, *Chemische Fabrik Uetikon*. TLC: silica gel 60, *Merck*, 0.25 mm, without fluorescence indicator; staining with basic $KMnO_4$. Specific rotation: *Perkin-Elmer-241* polarimeter, d = 10 cm, room temperature, concentration in g/100 mL, estimated error: ±5 %. IR ($CHCl_3$): selected bands in cm^{-1}, *br* = broad. NMR ($CDCl_3$): δ in ppm *vs.* TMS, *J* in Hz; ^1H: 300 MHz; ^{13}C: 75 MHz, assignments based on DEPT or APT spectra. MS: selected peaks; *m/z* (%); matrix for FAB-MS: 3-nitrobenzyl alcohol.

Synthesis of 5-Aza-Semicorrin 11 (Scheme 2). *(S)-5-[(tert-Butyl)dimethylsilyloxy]methyl-2-pyrrolidinone.* A mixture of 15.0 g (0.130 mol) of **7**, 39.2 g (0.260 mol) of (*tert*-butyl)dimethylchlorosilane, and 35.4 g (0.520 mol) of imidazole in 100 mL of DMF was stirred for 36 h at 42 °C.[19] After aqueous work-up with 600 mL of water, extraction with dichloromethane, and removal of the solvent, the resulting yellow oil was chromatographed with hexane/EtOAc 1:1 (10 cm x 18 cm column) to give 26.1 g (88%) of a colorless oil. In an analogous experiment, the crude product was purified by distillation at 0.05 Torr (b.p.175-180 °C). The yield and purity of the distilled product were the same as in this experiment. Analytical data: $[\alpha]_D$ = +50 (c=1.1, $CHCl_3$). IR: 3430*m*, 1690*s*, 1470*m*, 1460*m*, 1415*m*, 1390*m*, 1365*w*, 1310*w*, 1255*s*, 1110*s*(*br*), 1005*m*, 835*s*. ^{1}H-NMR: 0.05 (*s*, $SiMe_2$); 0.88 (*s*, $SiCMe_3$); 1.67-1.79/2.10-2.22 (*m*, H_2C); 2.25-2.36 (*m*, H_2C); 3.43 (*dd*, *J* = 7.7, 10.0, *H*HC-O); 3.61 (*dd*, *J* = 4.0, 10.0, H*H*C-O); 3.70-3.78 (*m*, HC); 5.89 (*br s*, NH). ^{13}C-NMR: -5.4 ($SiMe_2$); 18.2 (Si*C*Me_3); 22.8 (H_2C); 25.8 (Si*C*Me_3); 29.8 (H_2C); 55.8 (HC); 66.9 (H_2C-O); 178 (CO). MS (EI): 173(13), 172(100, M^+-C_4H_9). TLC (hexane/EtOAc 1:1): R_f = 0.13.

(S)-5-[(tert-Butyl)dimethylsilyloxy]methyl-2-thiopyrrolidinone. A mixture of 25.4 g (0.111 mol) of (*S*)-5-[(*tert*-butyl)dimethylsilyloxy]methyl-2-pyrrolidinone and 23.9 g (0.059 mol) of Lawesson's reagent[10] in 320 mL of THF was stirred for 2 h at room temperature. After removal of the solvent, the residue was chromatographed on a 10 cm x 15 cm column with hexane/EtOAc 4:1 to give 23.5 g (86 %) of a colorless oil which solidified upon standing. After recrystallization from hexane at -20 °C, the yield was 20.5 g (76 %). Analytical data: m.p. 60-61 °C. $[\alpha]_D$ = +84 (c=1.2, $CHCl_3$). IR: 3400*m*, 1500*s*, 1470*m*, 1460*m*, 1420*m*, 1390*w*, 1360*m*, 1310*m*, 1255*s*, 1105*s*, 1075*m*, 1020*m*, 1005*m*, 970*w*, 935*w*, 835*s*. ^{1}H-NMR: 0.07 (*s*, $SiMe_2$); 0.89 (*s*, $SiCMe_3$); 1.76-1.88/2.19-2.31 (*m*, H_2C); 2.84-2.98 (*m*, H_2C); 3.50 (*dd*, *J* = 8.1, 10.3, H*H*C-O); 3.69 (*dd*, *J* = 3.8, 10.3, *H*HC-O); 3.98-4.07 (*m*, HC); 7.88-7.91 (*br s*, NH). ^{13}C-NMR: -5.4 ($SiMe_2$); 18.2 (Si*C*Me_3); 25.0 (H_2C); 25.8 (Si*C*Me_3); 42.9 (H_2C); 64.0 (HC); 65.7 (H_2C-O); 205.8 (CS). MS (EI): 245 (3, M^+), 189(14), 188(100), 172(16). TLC (hexane/EtOAc 4:1): R_f = 0.27. Anal. calc. for $C_{11}H_{23}NOSSi$: C = 53.83, H = 9.44, N = 5.71; found: C = 53.86, H = 9.19, N = 5.72.

Thioimidate (*S*)-**8**. 30 mL of freshly distilled methyl iodide were added to a solution of 11.3 g (0.046 mol) of (*S*)-5-[(*tert*-butyl)dimethylsilyloxy]methyl-2-thiopyrrolidinone in 45 mL of dichloromethane. After stirring for 75 min at room temperature under argon, the mixture was concentrated *in vacuo*. The resulting solid was ground in a mortar to give a yellowish powder which was dried for 6 h at 0.05 Torr (m.p. 105-106 °C). The product was dissolved in 200 mL of dichloromethane and extracted with saturated aqueous $NaHCO_3$ solution. The organic layer was filtered through cotton and concentrated *in vacuo* to give 10.7 g (90 %) of a colorless oil which partially solidified upon standing. Analytical data: IR: 1590*s*, 1470*m*, 1460*m*, 1425*w*, 1390*w*, 1360*w*, 1300*m*, 1255*s*, 115*m*, 1090*s*, 1070*s*, 1050*m*, 1020*m*, 1005*m*, 975*w*, 960*w*, 935*w*, 900*w*, 880*m*, 835*s*. ^{1}H-NMR: 0.03/0.04 (*s*, $SiMe_2$); 0.87 (*s*, $SiCMe_3$); 1.87-2.13 (*m*, H_2C); 2.44 (*s*, SCH_3); 2.49-2.70 (*m*, H_2C); 3.63 (*dd*, *J* = 5.4, 10.1, H*H*C-O); 3.81 (*dd*, *J* = 3.8, 10.1, *H*HC-O); 4.13-4.18 (*m*, HC). TLC (hexane/EtOAc 2:1): R_f = 0.69.

Amidine (*S*)-**9**. A mixture of 10.5 g (0.040 mol) of **8** and 2.2 g (0.042 mol) of NH_4Cl in 74 mL of anhydrous methanol was refluxed for 2 h under argon. The solvent was removed (caution: evolution of methylmercaptan) and the residue was dissolved in dichloromethane. Filtration and concentration *in vacuo* gave a white solid which was washed with cold hexane. This product (10.1 g, 95%, m.p. 186-187 °C) had the same analytical data as a sample obtained by recrystallization from dichloromethane/hexane. M.p. 186-187 °C. $[\alpha]_D$ = +20.2 (c=1.3, $CHCl_3$). IR: 3500-2700*m*(*br*), 1690*s*, 1600*w*(*br*), 1500*w*(*br*), 1470*m*, 1460*m*, 1420*w*, 1360*w*, 1340*w*, 1310*w*, 1255*m*, 1120*m*, 865*m*, 835*s*. ^{1}H-NMR: 0.06/0.07 (*s*, $SiMe_2$); 0.88 (*s*, $SiCMe_3$); 1.92-2.03/2.17-2.30 (*m*, H_2C); 2.90-3.01 (*m*, H_2C); 3.60 (*dd*, *J* = 4.8, 10.7, H*H*C-O); 3.69 (*dd*, *J* = 4.0, 10.7, *H*HC-O); 3.99-4.07 (*m*, HC); 8.8-9.0 (*br s*, NH); 9.2-9.6 (*br s*, NH_2). ^{13}C-NMR: -5.5/-5.4 ($SiMe_2$); 18.2 (Si*C*Me_3); 23.0 (H_2C); 25.8 (Si*C*Me_3); 30.2 (H_2C); 61.4 (HC); 64.9 (H_2C-O); 172.0 (CN). MS (EI): 213(5),

172(14), 171(100). TLC (CH_2Cl_2/EtOH 9:1): R_f = 0.10. Anal. calc. for $C_{11}H_{25}N_2OClSi$: C = 49.88, H = 9.51, N = 10.58; found: C = 49.35, H = 9.02, N = 10.64.

5-Aza-semicorrin (*S,S*)-**10**. To a suspension of 1.37 g (5.2 mmol) of **9** in 5.0 mL of THF at 0 °C, a solution of butyllithium (1.76 M in hexane, 2.64 mL, 4.6 mmol, 0.90 equiv.) was slowly added under argon. After stirring for 5 min at room temperature, the resulting homogeneous solution was combined with a solution of 1.34 g (5.2 mmol) of **8** in 2.5 mL of THF. The solvent was removed at 0.1 Torr and the resulting yellowish oil was heated at 72 °C for 24 h in an evacuated ampule sealed with a Teflon stopper. The reaction was monitored by UV-spectroscopy (λ_{max} of **10** at 255 nm). After work-up with saturated aqueous $NaHCO_3$ solution and extraction with Et_2O, the crude product was chromatographed (6 cm x 15 cm column) with Et_2O/EtOH 9:1 to give 1.30 g (57 %) of a colorless oil. Analytical data: $[\alpha]_D$ = -77 (c=1.4, $CHCl_3$). IR: 3740-3630*w(br)*, 3620-3560*w(br)*, 1605*s*, 1550*s*, 1470*m*, 1460*m*, 1430*w*, 1415*w*, 1385*w*, 1360*m*, 1335*m*, 1315*w*, 1305*w*, 1260*s*, 1110*s(br)*, 1005*m*, 935*w*, 835*s*. ^{1}H-NMR: 0.03/0.05 (*s*, $SiMe_2$); 0.89 (*s*, $SiCMe_3$); 1.62-1.74/1.95-2.07 (*m*, H_2C); 2.53-2.72 (*m*, H_2C); 3.54/3.65 (AB part of ABX, J_{AB} = 10.0, J_{AX} = 5.9, J_{BX} = 5.8, H_2C-O); 3.97-4.05 (*m*, X part of ABX, HC). ^{13}C-NMR: -5.32/-5.28 ($SiMe_2$); 18.3 ($SiCMe_3$); 23.8 (H_2C); 25.9 ($SiCMe_3$); 34.7 (H_2C); 65.6 (HC); 67.0 (H_2C-O); 173.4 (CN). MS (EI): 439(0.4, M^+), 383(6), 382(19), 296(6), 295(23), 294(100). UV(EtOH): 255 (10500). TLC (Et_2O/EtOH 9:1): R_f = 0.23.

5-Aza-semicorrin (*S,S*)-**11** [*(S,S)-Bis{2-[((tert-butyl)dimethylsilyloxy)methyl]-3,4-dihydro-2H-pyrrol-5-yl}(methyl)amine*]. A solution of 377 mg (0.86 mmol) of **10** in 5.7 mL of freshly distilled methyl iodide was degassed at 0.01 Torr by three freeze-thaw cycles and stirred at room temperature in the dark for 1 h under argon in an ampule sealed with a Teflon stopper. After concentration *in vacuo*, the resulting colorless oil was shaken with hexane in order to induce crystallization. Shaking was continued until crystallization was complete. After filtration and washing with cold hexane, the remaining solid was pulverized in a mortar and dried at 0.01 Torr to give 394 mg (79 %) of a white powder (m.p. 110-111 °C) with the same analytical data as a sample obtained by recrystallization from hexane/EtOAc at -20 °C (m.p. 110-111 °C). **11**·HI: $[\alpha]_D$ = -32 (c=1.4, $CHCl_3$). IR: 1660*s*, 1605*s*, 1495*m*, 1470*m*, 1460*m*, 1430*w*, 1410*w*, 1390*w*, 1360*w*, 1335*w*, 1310*w*, 1260*m*, 1115*s*, 1005*w*, 940*w*, 840*s*. ^{1}H-NMR: 0.05/0.07 (*s*, $SiMe_2$); 0.88 (*s*, $SiCMe_3$); 1.98-2.10/2.23-2.35 (*m*, H_2C); 3.13-3.38 (*m*, H_2C); 3.66 (*s*, NCH_3); 3.70-3.79 (*m*, H_2C-O); 4.30-4.36 (*m*, HC); 12.9 (*br s*, NH). ^{13}C-NMR: -5.4/-5.3 ($SiMe_2$); 18.1 ($SiCMe_3$); 22.7 (H_2C); 25.7 ($SiCMe_3$); 34.7 (H_2C); 39.6 (NCH_3); 65.4 (H_2C-O); 68.0 (HC); 170.0 (CN). MS (EI): 453(1.7, M^+-HI), 397(16), 396(48), 309(24), 308(100). UV (EtOH): 221 (16200). TLC (Et_2O/EtOH 4:1): R_f = 0.24. Anal. calc. for $C_{23}H_{48}N_3O_2ISi$: C = 47.49, H = 8.32, N = 7.22; found: C = 46.90, H = 8.20, N = 7.18.

The hydroiodide was dissolved in dichloromethane and extracted with saturated aqueous $NaHCO_3$ solution. The organic layer was filtered through cotton and concentrated *in vacuo* to afford the neutral ligand **11** as a colorless oil in quantitative yield. Analytical data: $[\alpha]_D$ = +10.3 (c=1.2, $CHCl_3$). IR: 1605*s*, 1585*s*, 1470*m*, 1460*m*, 1425*m*, 1400*s*, 1360*m*, 1335*w*, 1310*m*, 1260*s*, 1110*s(br)* 1005*m*, 840*s*. ^{1}H-NMR: 0.03/0.05 (*s*, $SiMe_2$); 0.87 (*s*, $SiCMe_3$); 1.76-2.10 (*m*, H_2C); 2.79-2.87 (*m*, H_2C); 3.32 (*s*, NCH_3); 3.50/3.79 (AB part of ABX, J_{AB} = 9.9, J_{AX} = 6.0, J_{BX} = 4.0, H_2C-O); 3.98-4.05 (*m*, X part of ABX, HC). ^{13}C-NMR: -6.4 ($SiMe_2$); 17.3 ($SiCMe_3$); 24.9 ($SiCMe_3$); 25.3 (H_2C); 34.0 (H_2C); 35.0 (NCH_3); 66.0/68.5 (H_2C-O/HC); 166.3 (CN). UV(EtOH): 243 (11300). TLC (Et_2O/EtOH 4:1): R_f = 0.03-0.09.

Synthesis of 5-Aza-Semicorrins 13 and 14 (Scheme 3). *(S)-5-(1-Hydroxy-1-methylethyl)-2-pyrrolidinone* **12**. To a vigorously stirred solution of 11.2 g (78 mmol) of L-pyroglutamic acid methyl ester in 150 mL of THF under N_2 at room temperature, was added a 3.0 M solution of MeMgBr in diethylether (65 mL; 0.19 mol). After 3 h at reflux, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and repeatedly extracted with THF. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*.

Chromatography (5 cm x 20 cm column) with CH_2Cl_2/MeOH (19:1 → 9:1) afforded 5.4 g (48 %) of **12** as a white crystalline solid. The analytical data were obtained from a sample recrystallized from EtOAc/pentane. $[\alpha]_D$ = 1.01 (c=0.97, EtOH). M.p. 64-66 °C. IR: 3400*m*, 1680*s*, 1520*m*, 1470*w*, 1420*m*, 1330*w*, 1210*s*, 1090*w*, 1020*w (br)*, 930*m*, 870*w*, 850*m*, 800*s(br)*. ^{1}H-NMR: 1.15/1.22 (*s*, Me); 1.91-2.16 (*m*, H_2C); 2.30-2.73 (*m*, H_2C); 2.73 (*s*, OH); 3.58 (*dd*, *J* = 6.1, 7.9, HC); 6.97 (NH). ^{13}C-NMR: 21.8 (H_2C); 23.1/26.2 (Me); 30.4 (H_2C); 63.5 (HC); 71.5 (CMe_2); 179.3 (CO). MS (EI): 144(100, M^++1), 126(28), 85(47), 84(37), 59(16), 57(15). TLC (CH_2Cl_2/MeOH 9:1): R_f = 0.22 .

5-Aza-semicorrin (*S,S*)-**13**. 1.87 g (13.0 mmol) of **12**, 8.2 mL (39 mmol) of bis(trimethylsilyl)amine, and 250 mg (1.31 mmol) of *p*-toluenesulfonic acid monohydrate were heated in an ampule for 20 h at 130 °C under argon. After concentration at 0.01 Torr/23 °C, the dark brown residue was dissolved in 3 mL of toluene and heated for another 7 h at 130 °C under argon. The mixture was treated with charcoal for 5 min at 130 °C and filtered through celite. After evaporation of the solvent, the brownish residue was chromatographed (5 cm x 18 cm column) with Et_2O/EtOH (9:1 → 4:1) to give 1.36 g (51 %) of a colorless oil, which crystallized upon standing at -20 °C. As a byproduct, 77 mg of the silylated starting material (**5**, R=CMe_2OSiMe_2t-Bu) was obtained, in addition to 192 mg of a (2:1) product/byproduct mixture. Analytical data: $[\alpha]_D$ = -175 (c=1.06, EtOH). IR: 3200-3050*w(br)*, 1600*s*, 1550*s*, 1460*w*, 1410*w*, 1380*w*, 1375*w*, 1360*m*, 1250*s*, 1170*s*, 1090*w*, 1040*s*, 900*m*, 890*m*, 850*s*, 840*s*. ^{1}H-NMR: 0.07 (*s*, $SiMe_3$); 1.18 /1.22 (*s*, CMe_2); 1.76-1.92 (*m*, H_2C); 2.55-2.61 (*m*, H_2C); 3.78 (*t*, *J* = 6.8, HC). ^{13}C-NMR: 2.5 ($SiMe_3$); 22.1 (H_2C); 26.0/26.9 (CMe_2); 35.0 (H_2C); 73.9 (HC); 75.7 (CMe_2); 173.1 (CN). MS (FAB): 413(40), 412(100, $(M+H)^+$), 281(7), 280(8). UV (EtOH): 255 (12100). TLC (CH_2Cl_2/MeOH 9:1): R_f = 0.37.

5-Aza-semicorrin (*S,S*)-**14**. Methylation of **13** in MeI/CH_2Cl_2 (1:1), as described for **10**, gave the hydroiodide of **14** in 81 % yield (57 % after recrystallization from EtOAc/pentane 4:1 at -20 °C). Analytical data for **14**·HI: $[\alpha]_D$ = -80 (c=1.05, EtOH). M.p. 169-170° C. IR: 1660*s*, 1605*s*, 1500*m*, 1460*w*, 1430*w*, 1390*w*, 1360*w*, 1340*w*, 1250*s*, 1180*m*, 1150*m*, 1040*m*, 910*m*, 840*s*, 660*m*. ^{1}H-NMR: 0.07 (*s*, $SiMe_3$); 1.24 (*s*, CMe_2); 2.02-2.09/2.12-2.23 (*m*, H_2C); 3.17-3.28 (*m*, H_2C); 3.67 (*s*, NCH_3); 4.07 (*t*, *J* = 7.0, HC); 12.85 (*br s*, NH). ^{13}C-NMR: 2.4 ($SiMe_3$); 21.7 (H_2C); 26.5/26.6 (CMe_2); 34.8 (H_2C); 39.7 (NCH_3); 74.9 (CMe_2); 76.3 (HC); 169.9 (CN). UV (EtOH): 243 (12400), 220 (20100). TLC (CH_2Cl_2/MeOH 9:1): R_f = 0.45. Anal. calc. for $C_{21}H_{44}N_3O_2ISi_2$: C = 45.56, H = 8.01, N = 7.59; found: C = 45.61, H = 8.07, N = 7.47.

The hydroiodide was converted to the neutral ligand **14** as described for **11**. Analytical data of **14** (colorless oil): $[\alpha]_D$ = -85 (c=1.25, EtOH). IR: 1610*s*, 1590*s*, 1460*w*, 1420*m*, 1400*s*, 1380*m*, 1360*m*, 1250*s*, 1200*s*, 1170*s*, 1130*m*, 1040*s*, 900*m*, 840*s*, 750*s*, 660*m*. ^{1}H-NMR: 0.09 (*s*, $SiMe_3$); 1.20/1.31 (*s*, CMe_2); 1.89-1.97 (*m*, H_2C); 2.66-2.77/2.88-2.99 (*m*, H_2C); 3.34 (*s*, NCH_3); 3.80 (*t*, *J* = 6.8, HC). ^{13}C-NMR: 2.6 ($SiMe_3$); 24.3 (H_2C); 25.8/28.7 (CMe_2); 35.4 (H_2C); 35.8 (NCH_3); 76.4 (CMe_2); 77.6 (HC); 166.5 (CN). MS (FAB): 427(36), 426(100, $(M+H)^+$), 295(7), 294(7). UV (EtOH): 245 (16500). TLC (CH_2Cl_2/MeOH 9:1): R_f = 0.13 .

Synthesis of 5-Aza-semicorrin 18. The lactam **12** was converted to **18** using the same procedures described above for the synthesis of **11** (cf. Scheme 2). *(S)-5-{1-[(tert-Butyl)dimethylsilyloxy]-1-methylethyl}-2-pyrrolidinone* **5** *(R=CMe_2OSiMe_2t-Bu)*. To a solution of (*S*)-**12** (1.63 g, 11.4 mmol) and 2,6-lutidine (6.6 mL, 57 mmol) in 200 mL of dichloromethane was slowly added 4.0 mL (17 mmol) of *tert*-butyldimethylsilyl triflate.[20] After stirring for 2.3 h under N_2, the reaction mixture was poured onto saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with 0.1 *N* HCl, saturated aqueous $NaHCO_3$, and saturated NaCl solution. After drying over Na_2SO_4, the solvent was removed and the remaining yellowish solid (3.45 g) was recrystallized from pentane at 0 °C to give 2.52 g (81 %) of white crystals. Analytical data: $[\alpha]_D$= -9.1 (c= 0.93, EtOH). M.p. 72 °C. IR: 3340*w*, 1690*s*, 1470*w*, 1460*w*, 1420*w*, 1390*w*, 1360*w*, 1260*m*, 1170*m*, 1030*w*, 1000*w*, 830*m*. ^{1}H-NMR: 0.10 (*s*, $SiCMe_3$); 0.85 (*s*, $SiMe_2$); 1.15/1.19 (*s*, CMe_2); 1.89-

1.95/2.02-2.13 (*m*, H_2C); 2.30-2.38 (*m*, H_2C); 3.53 (*dd*, *J* = 5.7, 8.5, HC); 7.26 (*s*, NH). ^{13}C-NMR: -2.2 ($SiMe_2$); 17.9 ($SiCMe_3$); 21.9 (H_2C); 24.1/26.1 (CMe_2); 25.7 ($SiCMe_3$); 30.3 (H_2C); 64.3 (HC); 74.8 (CMe_2); 178.7 (CO). MS (EI): 200(15), 199(92), 172(82), 75(66), 73(100). TLC (CH_2Cl_2/MeOH 9.1): R_f = 0.58. Anal. calc. for $C_{13}H_{27}O_2NSi$: C = 60.65, H = 10.57, N = 5.44; found: C = 60.43, H = 10.32, N = 5.14.

(S)-5-{1-[(tert-Butyl)dimethylsilyloxy]-1-methylethyl}-2-thiopyrrolidinone. Isolated in ~100 % yield after reaction with Lawesson's reagent and column chromatography with hexane/EtOAc 9:1. Analytical data of a sample recrystallized from hexane at -20 °C: $[\alpha]_D$ = -38 (c=0.87, EtOH). M.p. 42 °C. IR: 3420*m*, 1510*s*, 1470*m*, 1460*m*, 1420*w*, 1390*w*, 1370*w*, 1360*w*, 1300*w*, 1280*m*, 1260*s*, 1170*m*, 1150*w*, 1120*w*, 1080*w*, 1030*w*, 1005*m*, 940*w*, 910*w*, 840*s*. ^{1}H-NMR: 0.12 (*s*, $SiMe_2$); 0.87 (*s*, $SiCMe_3$); 1.17/1.24 (*s*, CMe_2); 1.95-1.98/2.16-2.23 (*m*, H_2C); 2.89-2.97 (*m*, H_2C); 3.81 (*t*, *J* = 7.4, HC); 7.75 (*br s*, NH). ^{13}C-NMR: -2.1 ($SiMe_2$); 18.0 ($SiCMe_3$); 24.3/26.6 (CMe_2); 24.4 (H_2C); 25.8 ($SiCMe_3$); 43.2 (H_2C); 72.3 (HC); 74.9 (CMe_2); 206.0 (CS). MS (EI): 274(12, $(M+1)^+$), 217(10), 216(60), 200(17), 174(14), 173(97), 115(20), 75(47), 74(11), 73(100). TLC (hexane/EtOAc 1:1): R_f = 0.63. Anal. calc for $C_{13}H_{27}ONSSi$: C = 57.09, H = 9.95, N = 5.12; found: C = 56.91, H = 10.01, N = 5.12.

Conversion to the Amidine. The thiolactam was *S*-methylated and converted to the corresponding amidine, as described for **9**. The overall yield of amidine hydrochloride was 95 %. Analytical data: $[\alpha]_D$ = -6.6 (c=1.04, EtOH). M.p. 187 °C. IR: 3690*w*, 3300-3000*m(br)*, 1690*s*, 1603*w*, 1509*w*, 1470*w*, 1460*w*, 1420*w*, 1390*w*, 1370*w*, 1250*m*, 1180*m*, 1150*m*, 1044*m*, 1006*m*, 890*w*, 837*m*, 812*m*. ^{1}H-NMR: 0.12 (*s*, $SiMe_2$); 0.85 (*s*, $SiCMe_3$); 1.23 /1.32 (*s*, CMe_2); 2.09-2.16 (*m*, H_2C); 2.80-2.97 (*m*, H_2C); 3.75 (*t*, *J* = 6.6, HC); 8.9 (*br s*, NH_2); 10 (*br s*, NH). ^{13}C-NMR: -2.2 ($SiMe_2$); 18.0 ($SiCMe_3$); 21.5 (H_2C); 25.8 ($SiCMe_3$); 26.5 (CMe_2); 30.2 (H_2C); 70.0 (HC); 74.0 (CMe_2); 172.0 (CN). MS (EI): 241(13), 200(23), 199(87), 174(34), 173(78), 73(100). Anal. calc. for $C_{13}H_{29}ON_2SiCl$: C = 53.38, H = 9.99, N = 9.58; found: C = 52.94, H = 9.32, N = 9.26.

5-Aza-semicorrin (S,S)-6 (R=CMe$_2$OSiMe$_2$t-Bu). Isolated in 37 % yield after column chromatography with Et_2O/EtOH 95:5 (reaction conditions and work-up: see preparation of **10**). Analytical data: $[\alpha]_D$ = -191 (c=1.06, EtOH). M.p. 51-53 °C. IR: 3200-3100*w(br)*, 1608*s*, 1560*s*, 1470*m*, 1460*m*, 1420*w*, 1380*w*, 1360*w*, 1250*w*, 1170*m*, 1140*w*, 1080*w*, 1050*m*, 1006*w*, 937*w*, 894*w*, 836*m*. ^{1}H-NMR: 0.05/0.07 (*s*, $SiMe_2$); 0.83 (*s*, $SiCMe_3$); 1.20/1.23 (*s*, CMe_2); 1.86-1.93 (*m*, H_2C); 2.59 (*t*, *J* ≈ 8.4, H_2C); 3.74-3.79 (*m*, HC). ^{13}C-NMR: -2.1/0.0 ($SiMe_2$); 18.1 ($SiCMe_3$); 21.9 (H_2C); 25.8 ($SiCMe_3$); 26.1/27.6 (CMe_2); 35.0 (H_2C); 74.0 (HC); 75.1 (CMe_2); 173.2 (CN). MS (EI): 496(<1, $(M+H)^+$), 322(100), 306(12). UV (EtOH): 255 (8700). TLC (EtOH/Et_2O 1:9): R_f = 0.59.

5-Aza-semicorrin (S,S)-18. Methylation of (*S,S*)-**6** (R = CMe_2OSiMe_2t-Bu) in MeI/CH_2Cl_2 1:1 gave a 63 % yield of the hydroiodide of **18** after recrystallization from EtOAc/pentane. **18**·HI: $[\alpha]_D$ = -65 (c=0.90, $CHCl_3$). M.p. 131 °C. IR: 1660*s*, 1600*s*, 1500*w*, 1470*w*, 1460*w*, 1430*w*, 1380*w*, 1360*w*, 1250*m*, 1170*m*, 1150*m*, 1040*s*, 1000*w*, 890*w*, 830*s*. ^{1}H-NMR: 0.09/0.11 (*s*, $SiMe_2$); 0.83 (*s*, $SiCMe_3$); 1.29/1.31 (*s*, CMe_2); 2.13-2.29 (*m*, H_2C); 3.17-3.23/3.28-3.34 (*m*, H_2C); 3.68 (*s*, NCH_3); 4.12 (*t*, *J* = 7.0, HC); 12.97 (*s*, NH). ^{13}C-NMR: -2.2 ($SiMe_2$); 18.0 ($SiCMe_3$); 21.5 (H_2C); 25.7 ($SiCMe_3$); 26.6/27.2 (CMe_2); 34.7 (H_2C); 40.2 (NCH_3); 74.5 (HC); 76.5 (CMe_2); 170.2 (CN). MS (FAB): 512(16), 511(41), 510(100, $(M-I)^+$). UV (EtOH): 243 (16400), 221 (22600). TLC (Et_2O/EtOH 4:1): R_f = 0.35-0.47. Anal. calc. for $C_{27}H_{56}O_2N_3Si_2I$: C = 50.84, H = 8.85, N = 6.59; found: C = 50.39, H = 8.33, N = 6.48.

Data of the neutral ligand **18** (colorless oil): $[\alpha]_D$ = -72 (c=1.04, EtOH). IR: 1660*m*, 1610*m*, 1590*m*, 1470*m*, 1460*m*, 1390*s*, 1370*m*, 1360*m*, 1250*s*, 1160*m*, 1130*m*, 1040*s*, 1000*w*, 890*w*, 830*s*. ^{1}H-NMR: 0.05/0.08 (*s*, $SiMe_2$); 0.82 (*s*, $SiCMe_3$); 1.21 /1.28 (*s*, CMe_2); 1.89-1.98 (*m*, H_2C); 2.67-2.78/2.90-3.01 (*m*,

H_2C); 3.33 (*s*, NCH_3); 3.77 (*t*, *J* = 7.0, HC). ^{13}C-NMR: -2.1 ($SiMe_2$); 18.1 ($SiCMe_3$); 24.0 (H_2C); 25.8 ($SiCMe_3$); 26.1/28.7 (CMe_2); 35.5 (H_2C); 35.7 (NCH_3); 75.9 (CMe_2); 77.9 (HC); 166.2 (CN). MS (CI): 512(15), 511(42), 510(100, $(M+H)^+$), 378(13), 272(11), 271(55), 258(14), 242(40). UV (EtOH): 245 (17700). TLC (Et_2O/EtOH 4:1): R_f = 0.17-0.34.

Copper-Catalyzed Cyclopropanation (Table 1). *General procedure* (*cf.* ref. 8b). All steps were carried out under an argon atmosphere. To 3.7 mg (15 μmol) of copper(I) triflate benzene complex [Cu(I)(OTf)(C_6H_6)$_{0.5}$] was added a solution of 16.5 μmol of ligand **11**, **14**, or **18** in 1 mL of 1,2-dichloroethane (or chloroform). The suspension was stirred at room temperature for 1 h. The resulting greenish solution was filtered through a cannula containing a plug of glass wool. After addition of styrene (1 mmol), a solution of the diazo compound (1.3 mmol) in 1 mL of 1,2-dichloroethane (or chloroform) was slowly added over a period of 2-6 h using a syringe pump. After stirring at room temperature overnight, the mixture was concentrated *in vacuo* to give a greenish oil which was chromatographed (1 cm x 13 cm column) with hexane/EtOAc 95:5. The resulting mixture of trans- and cis-cyclopropanecarboxylates **19** and **20** (R=ethyl, *tert*-butyl, menthyl) was analyzed by GC. The analytical data of the products are listed in ref. 4. The enantiomeric excess of the ethyl esters was determined by capillary GC with a chiral column (heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin in OV 1701-vinyl, 26m; 90° C, 0.3° C/min, 0.6 bar H_2; (1*S*,2*S*)/(1*R*,2*R*)-**19**: 71.7/70.5 min; (1*S*,2*R*)/(1*R*,2*S*)-**20**: 62.5/65.0 min).[21] For determining the enantiomeric excess, the *tert*-butyl esters were converted to the ethyl esters by transesterification (EtOH, H_2SO_4, reflux). GC analysis of the menthyl esters is described in ref. 4.

Palladium-Catalyzed Allylic Alkylation (Table 2). *General Procedure*. To 1.39 mg (3.80 μmol; 0.5 mol%) of [(η^3-C_3H_5)PdCl]$_2$[22] in a 30 mL ampule equipped with a magnetic stirring bar was added a solution of 4.31 mg (9.50 μmol, 1.25 mol%) of ligand **11** in 0.40 mL of methylene chloride. The suspension was degassed at 0.01 Torr by three freeze-thaw cycles. The evacuated ampule was sealed with a vacuum-tight Teflon stopper and the solution was stirred at 50 °C for 2 h. The resulting clear, colorless solution was treated successively with a solution of 193 mg (0.76 mmol) of *rac*-**21**[16a] in 2 mL of methylene chloride, 301 mg (2.28 mmol) of dimethyl malonate, 464 mg (2.28 mmol) of *N*,*O*-bis(trimethylsilyl)acetamide,[18] and 0.75 mg (7.6 μmol) of anhydrous potassium acetate. The colorless and - apart from insoluble potassium acetate - clear solution was immediately degassed by three freeze-thaw cycles. The evacuated ampule was sealed with a vacuum-thight Teflon stopper. The reaction mixture, which turned bright yellow and slightly turbid within a few minutes, was stirred at room temperature. After 118 h, conversion was complete according to TLC analysis (hexane/EtOAc 3:1, R_f(**21**) = 0.42, R_f(**22**) = 0.30, R_f(dimethyl malonate) = 0.22). The pale yellow, turbid reaction mixture was diluted with 100 mL of diethyl ether, transferred to a separatory funnel, and washed twice with ice-cold saturated aqueous NH_4Cl solution. The organic phase was dried over $MgSO_4$, concentrated *in vacuo*, and chromatographed (4 cm x 26 cm column, hexane/EtOAc 3:1) to afford 242 mg (97 %) of analytically pure (+)-**22** as a colorless, opaque oil (occasionally, the product solidified upon scratching with a spatula). The enantiomeric excess was determined by ^{1}H-NMR spectroscopy[16c] ($CDCl_3$, 300 MHz, 0.5 equiv. of Eu(hfc)$_3$, for one of the two CO_2CH_3-singlets (the one at lower field) a splitting with Δδ = 0.08 ppm was observed). Analytical data of (+)-(*R*)-**22** (*cf.* ref. 16a,c): $[\alpha]_D$ = +19.2 (c=1.30, $CHCl_3$); +16.4 (c=1.27, EtOH)[23]; 95 %ee (^{1}H-NMR, Eu(hfc)$_3$). IR: 1765*s*, 1740*s*, 1605*w*, 1500*m*, 1460*m*, 1440*s*, 1325*m*, 1265*s*, 1170*s*, 1025*w*, 965*m*. ^{1}H-NMR: 3.51 (*s*, Me); 3.70 (*s*, Me); 3.95 (*d*, *J* = 10.8, HC(2)); 4.27 (*dd*, *J* = 8.4, 10.7, HC(3)); 6.33 (*dd*, *J* = 8.4, 15.8, HC(4)); 6.49 (*d*, *J* = 15.6, HC(5)); 7.19-7.32 (*m*, 2 C_6H_5). ^{13}C-NMR: 49.1 (HC(2)); 52.4/52.6 (Me); 57.6 (HC(3)); 126.3/127.1/127.5/127.8/128.4/128.7/ 129.1/131.8 (aromat. CH, HC=CH); 136.8/140.1 (aromat. C); 167.7/168.1 (CO). MS (EI): 324 (12, M^+), 292(8), 264(9), 232(13), 205(78), 193(100).

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23. The $[\alpha]_D$-values reported for **22** vary considerably: 5.2 (c=1.4-1.8, EtOH, 48 %ee)[16c], 16.0 (c=3.2, EtOH, 75 %ee)[17b].
24. Under the same conditions using 1 mol% of catalyst and activation with phenylhydrazine, the selectivity was lower and less reproducible (70-80% ee for **19**, 60-65% ee for **20**). Thermal activation of the catalyst led to selectivities of 85 and 68% ee for **19** and **20** (1 or 2 mol% of **15**).[4] With menthyl diazoacetate, the selectivities were always the same, irrespective of the method of activation and the amount of catalyst (1-3 mol%).
25. According to our experiments with catalyst **16** (see ref. 9), the absolute configuration of **20** is (1*R*,2*S*) rather than (1*S*,2*R*) as reported in ref. 8a. Our assignment is based on GC comparison of the *l*-menthyl ester with a sample of known absolute configuration which was available from our previous work described in ref. 4.