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Chiral Mercaptoaryl-oxazolines as Ligands in Enantioselective Copper-Catalyzed 1,4-Additions of Grignard Reagents to Enones

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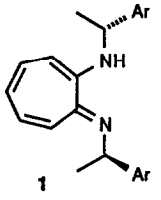
Abstract: A series of chiral enantiomerically pure mercaptoaryl-oxazolines has been synthesized. Copper(I) thiolate complexes derived from these ligands proved to be efficient catalysts for the 1,4-addition of Grignard reagents to cyclic enones. Enantioselectivities increased in the sequence cyclopentenone (16-37% ee) < cyclohexenone (60-72% ee) < cycloheptenone (83-87% ee).

INTRODUCTION

The conjugate addition of organocopper reagents to α,β-unsaturated carbonyl componds is a well-established, widely used process in organic synthesis.[1] One of the principal goals of current research in this field is the development of chiral copper reagents or catalysts, which selectively add to one of the two enantiotopic faces of a planar enone system.[2] In recent years, various cuprates with non-transferable chiral ligands have been described, which undergo enantioselective 1,4-addition, and in some cases, remarkable enantiomeric excesses exceeding 90% have been achieved.[3,4] However, synthetically useful methods, which require catalytic rather than stoichiometric amounts of a chiral copper complex, are still lacking. Only few examples of copper-catalyzed 1,4-additions have been reported which proceed with significant enantioselectivity.



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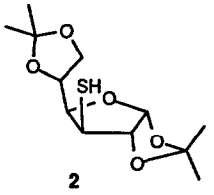

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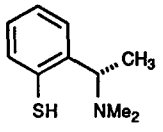

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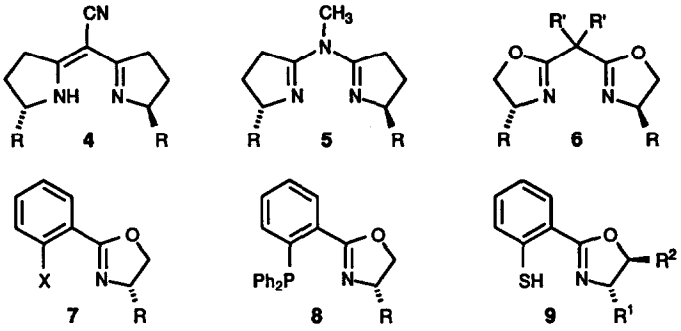
Lippard *et al.*[5] obtained up to 74% ee in the addition of *n*-butylmagnesium chloride to cyclohexenone catalyzed by copper(I) complexes of chiral aminotropone imines **1**. Similarly, with the thiosugar derivative **2** as chiral ligand, Spescha[6] obtained up to 60% ee. Another promising class of catalysts, copper(I) complexes with amino thiolates, has been developed by van Koten and coworkers.[7] The catalyst prepared from ligand **3** afforded up to 70-80% ee in the reaction of methylmagnesium iodide with benzylideneacetone.[7d]

We became interested in copper-catalyzed 1,4-additions in the course of our studies of chiral semicorrin ligands **4**.[8] We found that (semicorrinato)Cu(I) complexes derived from ligand **4** (R = CMe_2OH) are efficient catalysts for the cyclopropanation of olefins with diazo compounds.[8,9] We hoped that complexes of this type could also be used as enantioselective catalysts for conjugate addition. However, screening of various

(semicorrinato)copper complexes as catalysts in the reaction of 2-cyclohexenone or 1,3-diphenyl-2-propenone with Grignard reagents consistently gave racemic products. When the anionic ligands **4** were replaced by neutral aza-semicorrins **5**,[10] enantiomeric excesses of 10-15% ee were obtained.[11] Yet, despite extensive variation of the reaction conditions and the ligand structure, the selectivities could not be improved.

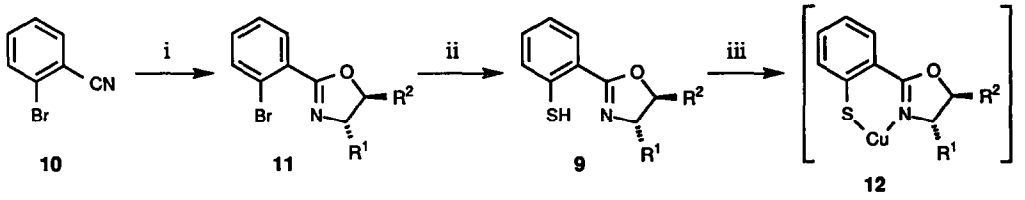


Subsequent studies led us to structurally related C_2-symmetric bisoxazoline ligands **6**[8,12] and, more recently, to non-symmetric oxazoline derivatives of type **7** (X = NR_2, PR_2, SH).[13-15] Ligands of this kind are readily prepared in enantiomerically pure form, starting from commercially available amino alcohols and aryl-carboxylic acid derivatives. The phosphinoaryl-oxazolines **8**,[14] which were also investigated in the laboratories of Helmchen[16] and Williams[17a], were found to be highly efficient ligands for enantioselective Pd-catalyzed allylic alkylations. In view of the promising results obtained with amino thiols **3**[7], we chose to study analogous mercaptophenyl-oxazolines **9** as controller ligands for enantioselective Cu-catalyzed 1,4-additions.

SYNTHESIS OF CHIRAL MERCAPTOPHENYL-OXAZOLINES

Mercaptophenyl-oxazolines **9** were synthesized from amino alcohols and 2-bromobenzonitrile, using the two-step sequence shown in Scheme 1. Zinc-catalyzed condensation of **10** with amino alcohols according to the method of Witte and Seeliger[18] afforded the corresponding oxazolines **11** in 50-80% yield. Lithium-bromine exchange with *n*-butyllithium, followed by reaction with elemental sulfur[7b,19] and subsequent work-up with aqueous acid, led to the desired ligands **9** in 30-60% yield. Starting from commercially available amino alcohols, a variety of differently substituted ligands is readily accessible in enantiomerically pure form by this route.

Scheme 1



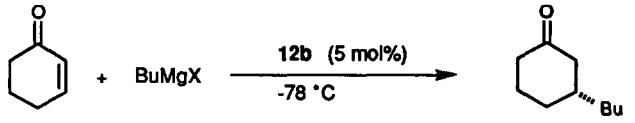
(i) amino alcohol, $ZnCl_2$ (2-5 mol%), chlorobenzene, reflux.
(ii) *n*-BuLi, THF, -78 °C; S_8, THF, -78 °C; HCl, H_2O.
(iii) *n*-BuLi, THF, -78 °C; CuI, THF, -20 °C.

a	$R^1 = CH_3$	$R^2 = H$
b	$R^1 = i$-Pr	$R^2 = H$
c	$R^1 = t$-Bu	$R^2 = H$
d	$R^1 = CH_2Ph$	$R^2 = H$
e	$R^1 = CH_2OSiMe_2t$-Bu	$R^2 = Ph$

CONJUGATE ADDITION TO 2-CYCLOHEXENONE

Copper(I) thiolate complexes derived from ligands **9** proved to be efficient catalysts for the conjugate addition of Grignard reagents to cyclic enones. For optimizing the reaction conditions, the 1,4-addition of *n*-butylmagnesium halides to cyclohexenone was chosen (Table 1). The catalysts were generated *in situ* from the corresponding ligand by deprotonation with *n*-butyllithium and subsequent complexation with CuI.[20] The best results were obtained when the Grignard reagent was slowly added at -78 °C to a THF solution containing the catalyst, the substrate, and 2 equiv. of hexamethyl phosphoric triamide (HMPA). Under these conditions, 3-butylcyclohexanone was formed in good yield, with high regioselectivity (>94% 1,4- *vs.* 1,2-addition) and an enantiomeric excess of 60%. Very similar results were obtained using butylmagnesium bromide instead of the chloride.

Table 1. 1,4-Addition of *n*-BuMgX to 2-Cyclohexenone: Influence of Solvent and Additives



Grignard Reagent	Solvent / Additives[b]	Yield [%]	ee[a] [%]
n-BuMgCl	THF	68	16
"	Et_2O	13	16
"	Et_2O/HMPA	34	34
"	Toluene/HMPA	68	47
"	THF/HMPA	67	60
"	THF/DMI	86	53
"	THF/DBU	36	49
"	THF/TMEDA	48	25
"	THF/Me_3SiCl	44	5
"	THF/HMPA /Me_3SiCl	37	7
"	THF/HMPA /Ph_2(*t*-Bu)SiCl	36	55
n-BuMgBr	THF/HMPA	65	54

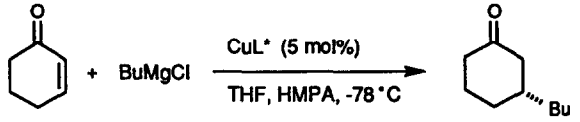
a) Determined by ^{13}C-NMR analysis after ketalization with (*R,R*)-(–)-2,3-butanediol.[23] All products had positive $[\alpha]_D$-values. Based on the sign of optical rotation, the configuration of 3-butylcyclohexanone is (*R*).[3a,24] b) 2 Equiv. of each additive with regard to the substrate was used. TMEDA: *N,N,N',N'*-tetramethyl-ethylenediamine; HMPA, DBU, DMI: see text.

It is well known that the solvent as well as polar additives, such as HMPA, and trialkylchlorosilanes can have a strong influence on the reactivity and selectivity of organocopper compounds.[21] In our case too, proper selection of the reaction medium was crucial. In pure THF or diethyl ether, the enantioselectivity was low. Substantially higher enantiomeric excesses were obtained in the presence of HMPA, DBU (1,8-

diazabicyclo[5.4.0]undec-7-ene), or DMI (1,3-dimethylimidazolidin-2-one), which was almost as effective as HMPA. In contrast to the findings of Lippard *et al.*[5], who recorded the highest enantioselectivity in the presence of HMPA and trialkylchlorosilanes, addition of Me_3SiCl resulted in a substantial loss of selectivity, whereas $Ph_2(t\text{-Bu})SiCl$ had no significant effect. Under optimum conditions (THF, 2 equiv. of HMPA), the observed enantiomeric excesses proved to be highly reproducible. In several experiments, the enantioselectivity of the addition of *n*-butylmagnesium chloride to cyclohexenone consistently ranged between 58 and 61% ee.

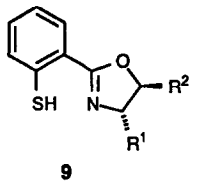
The copper(I) thiolate complex derived from ligand **9b** was isolated in analytically pure form by recrystallization from CH_2Cl_2/MeOH. The elemental analysis was in accord with formula $[(\mathbf{12b})_n]$. The principal peaks in the FAB mass spectrum can be assigned to dimeric and trimeric complexes. There are also strong signals which correspond to $[(\mathbf{12b})_3+Cu]$ and $[(\mathbf{12b})_4+Cu]$ fragments. Similar $[Cu_3L_3]$ and $[Cu_3L_3+Cu]$ species have been observed in the FAB mass spectrum of a copper(I) phosphine-thiolate complex by Togni et al.[7e] Our data are consistent with the structural studies of van Koten *et al.*[7] who showed that copper(I) amino thiolate complexes form aggregates with (Cu-S-Cu) bridges. In solution and in the solid state, the prominent species were found to be trimers containing a six-membered chair-like (Cu_3S_3)-ring. Unfortunately, the crystals of complex **12b**, that we obtained so far, were not suitable for x-ray structure analysis. When the recrystallized complex was used as catalyst, the resulting enantioselectivity was the same, within experimental error, as with the complex generated *in situ*.

Table 2. Enantioselective 1,4-Addition of *n*-BuMgCl to 2-Cyclohexenone: Comparison of Ligands



Ligand	R^1	R^2	Yield [%]	ee[a] [%]
9a	Me	H	39	58
9b	*i*-Pr	H	67	60
9c	*t*-Bu	H	46	15
9d	CH_2Ph	H	60	52
9e	$CH_2OSi(t\text{-Bu})Me_2$	Ph	45	47
13			76	60

a) See Table 1.



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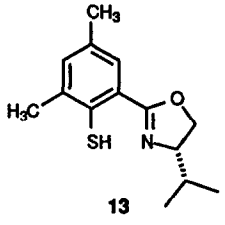

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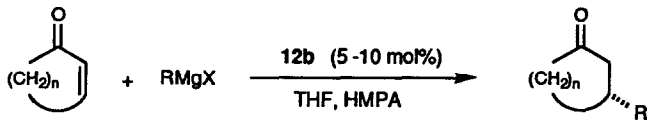
Table 2 shows a comparison of the different ligands **9a-e**. The methyl and isopropyl oxazolines **9a** and **9b** were found to be the most effective ligands, whereas the bulky *tert*-butyl derivative **9c** gave markedly lower enantioselectivities. Interestingly, introduction of a methyl group ortho to the thiol function had no effect. The dimethyl derivative **13** afforded exactly the same enantioselectivity as the parent ligand **9b**.

OTHER SUBSTRATES

In order to evaluate the scope of this catalyst system, other enones and Grignard reagents were examined. For cycloalkenones, enantioselectivites increased with ring size, from disappointingly low ee values for cyclopentenone to a maximum of 87% ee for cycloheptenone (Table 3). In all cases, addition occurred at the *Re* face. The same selectivity order for cyclic enones has also been observed with chiral amidocuprates.[2,3b] In the 1,4-additions to cycloheptenone, which was found to be less reactive than cyclohexenone, 10 rather than 5 mol% of catalyst proved to be necessary for obtaining satisfactory yields. The enantioselectivity, on the other hand, did not depend on the catalyst/substrate ratio. Isopropylmagnesium chloride gave consistently higher enantiomeric excesses than *n*-butylmagnesium chloride, whereas phenyl, methyl, and vinyl Grignard reagents reacted with poor enantioselectivity. Preliminary experiments with acyclic enones such as benzylideneacetone gave selectivities below 20% ee.

Table 3. Enantioselective 1,4-Addition of Alkylmagnesium Halides to Cycloalkenones



Enone	Catalyst [equiv.]	RMgX	Temp. [°C]	Yield [%]	ee[a] [%]
2-Cyclopentenone	0.05	*n*-BuMgCl	-78	30	16 (*R*)
„	0.05	*i*-PrMgCl	-78	43	37 (*R*)
2-Cyclohexenone	0.05	*n*-BuMgCl	-78	67	60 (*R*)
„	0.05	*i*-PrMgCl	-78	71	72 (*R*)
„	0.05	„	-45	89	68 (*R*)
2-Cycloheptenone	0.05	*n*-BuMgCl	-78	24	83 (*R*)
„	0.10	„	-78	50	83 (*R*)
„	0.10	*i*-PrMgCl	-78	55	87 (*R*)
„	0.10	„	-45	71	71 (*R*)

a) Determined by ^{13}C-NMR analysis after conversion to the corresponding ketals with (*R*,*R*)-(–)-2,3-butanediol.[23] All products had positive $[\alpha]_D$-values. According to the sign of optical rotation, the configuration of 3-butylcyclohexanone is (*R*).[3a,24] Configurational assignments of the other products are based on their CD spectra. The sign of the Cotton effect was found to be identical for all products, including (*R*)-(+)-3-methylcyclopentanone and (*R*)-(+)-3-methylcycloheptanone which served as reference compounds.[28]

Enantioselective catalysts or reagents, which form aggregates, often show a characteristic non-linear relationship beween their enantiomeric purity and the enantioselectivity induced by them.[22] Such non-linear effects have been rationalized as a consequence of different stability or reactivity of aggregates formed between homochiral monomers and those formed between heterochiral monomers. In our case too, experiments with samples of ligand **9b** with varying degrees of enantiomeric purity clearly showed a non-linear effect, the enantiomeric excess of the product beeing consistently lower than that of the ligand (Figure 1). However, the complex shape of the observed correlation curve and the lack of structural information about the catalyst preclude a straightforward interpretation of these results. Non-linear effects have been previously observed in conjugate additions of cuprates to enones. Rossiter *et al.*[3b] reported a weak positve deviation from linearity for the addition of an (amido)cuprate to cyloheptenone. Tanaka *et al.*[3c] observed a rather complex correlation for the reaction of a chiral (alkoxo)methylcuprate with (*E*)-2-cyclopentadecenone. For cuprates of low enantiomeric purity, the deviation from linearity was negative, but became positive for enantiomeric purities above 55% ee.

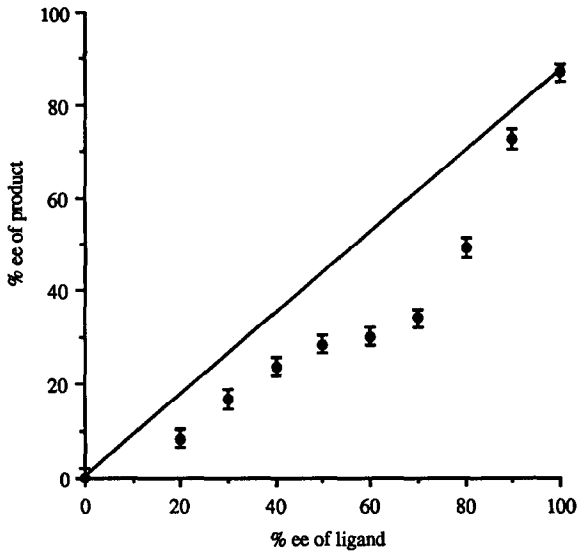


Figure 1. Addition of isopropylmagnesium chloride to 2-cycloheptenone catalyzed by **12b**. Correlation between the enantiomeric excesses of ligand **9b** and 3-isopropylcycloheptanone.

CONCLUSION

The results obtained with cycloheptenone are encouraging. For the first time, such high levels of enantioselectivity have been accomplished in a copper-catalyzed 1,4-addition. The selectivities with other enones, however, still need to be improved substantially. In order to achieve this goal, further modification of the ligand structure will be necessary. The ready access to mercaptoaryl-oxazolines such as **9** or **13**, and the wide variety of chiral amino alcohols available as starting materials, will facilitate such studies. However, further progress will also require a better understanding of the reaction mechanism and the catalyst structure. At present, no satisfactory model explaining the selectivity of (thiolato)copper catalysts **12** can be offered. Nevertheless, our results as well as van Koten's studies of amino thiols **3**[7] point to a considerable potential of chiral nitrogen-thiolate ligands for the enantiocontrol of copper-catalyzed conjugate addition reactions.

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EXPERIMENTAL

General: Et_2O and THF were distilled from Na/benzophenone. Toluene was distilled from Na. CuI: Merck, p. a. [CuBr(Me_2S)]: Fluka, purum. [Cu(OTf) (C_6H_6)$_{0.5}$]: Fluka, pract. 2-Bromobenzonitrile: Fluka, purum. Amino alcohols: Fluka, purum, except for L-*tert*-leucinol which was prepared by reduction of L-*tert*-leucine.[25] *n*-BuMgCl: Fluka (2.0 M in THF). *i*-PrMgCl: Aldrich (2.0 M in THF). All reactions were carried out under an argon atmosphere 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. Specific rotations were measured on a Perkin Elmer 241 polarimeter at room temperature, estimated error ±5%. IR ($CHCl_3$): selected bands in cm^{-1}. 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 Oxazolines 11. *General procedure*: *(4S)-4,5-Dihydro-2-(2'-bromophenyl)-4-methyl-oxazole* (**11a**). A mixture of 2.0 g (26.7 mmol) of L-alaninol, 4.85 g (26.7 mmol) of 2-bromobenzonitrile, and 136 mg (1 mmol) of anhydrous $ZnCl_2$ in 15 ml of chlorobenzene was refluxed for 24 h[18]. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography with hexane/EtOAc (3:1) to give 3.35 g of **11a** (52%) as a colorless oil. $[\alpha]_D = -51$ (c = 4.2, $CHCl_3$). IR: 1654s, 1591m, 1477m, 1438m, 1354s, 1303m, 1243m, 1112m, 1024s, 965s. ^1H-NMR: 1.38 (d, J = 6.7, 3H, CH_3), 3.96-4.05 (m, 1H, HC(5)), 4.27-4.48 (m, 1H, HC(4)), 4.49-4.57 (m, 1H, HC(5)), 7.26-7.35 (m, 2H, HC(4'), HC(5')), 7.61-7.70 (m, 2H, HC(3'), HC(6')). ^{13}C-NMR: 21.3 (CH_3), 62.3 (CH_2), 74.1 (CH), 121.7/126.9/129.9/131.2/131.4/133.6 (Ph), 162.7 (C=N). MS (EI): 241(43) 239(44, M^+/^{79}Br), 226(99), 224(100). TLC (hexane/EtOAc 3:1): R_f = 0.21. Anal. Calcd for $C_{10}H_{10}BrNO$: C, 50.00; H, 4.17; N, 5.83. Found: C, 50.10; H, 4.39; N, 6.09.

(4S)-4,5-Dihydro-2-(2'-bromophenyl)-4-isopropyloxazole (**11b**). Colorless oil, 78% yield. $[\alpha]_D = -62$ (c = 1.8, $CHCl_3$). IR: 1654s, 1588m, 1565w, 1471s, 1438s, 1354s, 1302m, 1241s, 1096s, 1026s, 960s. ^1H-NMR: 0.98 (d, J = 6.7, 3H, CH_3), 1.05 (d, J = 6.7, 3H, CH_3), 1.90 (m, 1H, HCMe$_2$), 4.14-4.19 (m, 2H, H_2C(5)), 4.38-4.46 (m, 1H, HC(4)), 7.25-7.35 (m, 2H, HC(4'), HC(5')), 7.62 (dd, J = 1.4, 8.0, 1H, HC(3' or 6')) 7.66 (dd, J = 2.2, 7.5, 1H, HC(6' or 3')). ^{13}C-NMR: 18.1 (CH_3), 18.7 (CH_3), 32.6 (CHMe$_2$), 70.2 (CH_2), 72.8 (HC(4)), 121.7/126.9/130.1/131.1/131.4/133.6 (Ph), 162.7 (C=N). MS (CI): 270(86), 268(91, M^++1/^{79}Br), 190(100). TLC (hexane/EtOAc 6:1): R_f = 0.39. Anal. Calcd for $C_{12}H_{14}BrNO$: C, 53.75; H, 5.26; N, 5.22. Found: C, 53.69; H, 5.46; N, 5.10.

(4S)-4,5-Dihydro-2-(2'-bromophenyl)-4-tert-butyloxazole (**11c**). Colorless oil, 50% yield. $[\alpha]_D = -87$ (c = 2.6, $CHCl_3$). IR: 1661s, 1589m, 1476s, 1435m, 1353s, 1246s, 1100s, 1026s, 962s. ^1H-NMR: 1.00 (s, 9H, *t*-Bu), 4.09 (dd, J = 7.9, 10.2, 1H, HC(5), 4.24 (t, J = 8.0, 1H, HC(4)), 4.36 (dd, J = 8.0, 10.2, 1H, HC(5)), 7.24-7.32 (m, 2H, HC(4'), HC(5')), 7.60-7.67 (m, 2H, HC(3'), HC(6')). ^{13}C-NMR: 25.8 (CH_3), 33.8 (CMe$_3$), 68.8 (CH_2), 76.6 (CH), 121.7/126.9/130.1/131.1/131.3/133.5 (Ph), 162.6 (C=N). MS (CI): 284(98), 282(100, M^++1/^{79}Br). TLC (hexane/EtOAc 15:1): R_f = 0.30. Anal. Calcd for $C_{13}H_{16}BrNO$: C, 55.33; H, 5.72; 4.96. Found: C, 55.45; H, 5.57; N, 5.00.

(4S)-4,5-Dihydro-2-(2'-bromophenyl)-4-benzyloxazole (**11d**). Colorless oil, 58% yield. $[\alpha]_D = -13.4$ (c = 3.3, $CHCl_3$). IR: 1656s, 1591m, 1478s, 1438s, 1357s, 1289w, 1092s, 1027s, 960s. ^1H-NMR: 2.83 (dd, J = 8.3, 13.8, 1H, CH_2Ph), 3.26 (dd, J = 5.3, 13.8, 1H, CH_2Ph), 4.20 (dd, J = 7.3, 8.5, 1H, HC(5)), 4.39 (dd, J = 8.5, 9.3, 1H, HC(5)), 4.63-4.68 (m, 1H, HC(4)), 7.25-7.38 (m, 7H, Ph), 7.63-7.70 (m, 2H, HC(3'), HC(6')). ^{13}C-NMR: 41.5 (CH$_2$Ph), 68.1 (H_2C(5)), 71.8 (HC(4)), 121.7/126.4/126.9/128.4/129.2/129.7/131.2/131.5/133.7/137.6 (Ph), 163.2 (C=N). MS (CI): 318(98), 316(100, M^++1/^{79}Br). TLC (hexane/EtOAc 5:1): R_f = 0.23. Anal. Calcd for $C_{16}H_{14}BrNO$: C, 60.76; H, 4.43; N, 4.43. Found: C, 60.78; H, 4.20; N, 4.57.

(4S,5S)-4,5-Dihydro-2-(2'-bromophenyl)-4-{[(tert-butyl)dimethylsilyloxy]methyl}-5-phenyloxazole (**11e**). (4*S*,5*S*)-4,5-Dihydro-2-(2'-bromophenyl)-4-(hydroxymethyl)-5-phenyloxazole was prepared in 57% yield according to the standard procedure described above. Colorless oil. $[\alpha]_D = +7.3$ (c = 1.8, $CHCl_3$). IR: 3329s, 1658s, 1590m, 1495m, 1477m, 1432m, 1333s, 1098s, 1026s, 963s. ^1H-NMR: 2.49 (m, 1H, OH), 3.75-3.85 (m, 1H, CH_2), 4.02-4.12 (m, 1H, CH_2), 4.34 (dt, J = 3.9, 7.8, 1H, HC(4)), 5.54 (d, J = 7.9, 1H,

HC(5)), 7.32-7.42 (m, 7H, Ph), 7.68 (dd, J = 1.5, 8.0, 1H, HC(3' or 6')), 7.76 (dd, J = 2.3, 7.4, 1H, HC(6' or 3')). ^{13}C-NMR: 63.8 (CH_2OH), 77.2(HC(5)), 83.3 (HC(4)), 121.9/125.9/127.2/128.5/128.9/129.5/131.3/131.9/133.9/ 140.1 (Ph), 164.3 (C=N). MS (CI): 334(99), 332(100, M^++1/^{79}Br), 254(88). TLC (Hexane/EtOAc 1:1): R_f = 0.32. Anal. Calcd for $C_{16}H_{14}BrNO_2$: C, 57.85; H, 4.25; N, 4.22. Found: C, 57.90; H, 4.17; N, 4.10.

The product (1.8 g, 5.4 mmol) was treated with 1.98 g (7.5 mmol) of *tert*-butyldimethylsilyl triflate and 2.67 g (25 mmol) of 2,6-lutidine in 50 ml of CH_2Cl_2. After stirring at room temperature for 1 h, 50 ml of saturated aqueous NH_4Cl was added. The resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with ice-cold 0.1 M HCl, saturated $NaHCO_3$ solution, H_2O, and saturated NaCl solution. Drying over Na_2SO_4, removal of the solvent, and concentration *in vacuo* afforded 2.25 g (93%) of **11e** as a colorless oil. $[\alpha]_D$ = +18.5 (c = 1.0, $CHCl_3$). IR: 1651s, 1589m, 1471s, 1435m, 1317m, 1256s, 1123s, 1097s, 1025s, 964s. ^{1}H-NMR: 0.12 (s, 6H, CH_3-Si), 0.93 (s, 9H, *t*-Bu), 3.80-3.87 (m, 1H, CH_2), 4.01-4.06 (m, 1H, CH_2), 4.29-4.35 (m, 1H, HC(4)), 5.61 (d, J = 8.0, 1H, HC(5)), 7.27-7.45 (m, 7H, Ph), 7.67 (dd, J = 1.5, 8.0, 1H, HC(3')), 7.80 (dd, J = 2.3, 7.5, 1H, HC(6')). ^{13}C-NMR: –5.3 (CH_3-Si), –5.2 (CH_3-Si), 18.3 (C-Si), 25.9 (CH_3-C), 64.8(CH_2), 77.7(HC(5)), 83.8 (HC(4)), 121.8/125.7/127.1/128/128.6/129.7/131.5/131.6/133.9/141.0 (Ph), 163.3 (C=N). MS (CI): 448(100), 446(94, M^++1/^{79}Br), 368(40). TLC (hexane/ EtOAc 6:1): R_f = 0.60. Anal. Calcd for $C_{22}H_{28}BrNO_2Si$: C, 59.19; H, 6.32; N, 3.14. Found: C, 59.30; H, 6.56; N, 3.24.

Synthesis of Mercaptophenyl-oxazolines 9. *General procedure: (4S)-4,5-Dihydro-2-(2'-mercaptophenyl)-4-methyloxazole* (**9a**). To 1.2 g (5 mmol) of **11a** in 30 ml of THF was added dropwise 3.5 ml (5.5 mmol) of *n*-BuLi (1.6 M in hexane) at -78 °C. The resulting solution was stirred at -78 °C for 10 min and then added through a cannula to a suspension of 160 mg (5 mmol) of sublimated sulfur in 20 ml of THF at -78 °C. The mixture was stirred at -78 °C for 3 h. After addition of 2.75 ml (5.5 mmol) of 2 M HCl, the mixture was allowed to warm up to room temperature. Extraction with Et_2O followed by flash column chromatography with hexane/EtOAc (3:1) gave 300 mg (31%) of **9a** as a yellow oil. $[\alpha]_D$ = -49 (c = 1.30, $CHCl_3$). IR: 2400m, 1638s, 1522s, 1422s, 1044s, 927s. ^{1}H-NMR: 1.23 (d, J = 7.0, 3H, CH_3), 4.09 (m, 1H, HC(5)), 4.52-4.63 (m, 2H, HC(4), HC(5)), 6.95 (t, J = 8.0, 1H, HC(5' or 4')), 7.10 (t, J = 8.1, 1H, HC(4' or 5')), 7.55 (d, J = 8.0, 1H, HC(3' or 6')), 7.80 (d, J = 8.1, 1H, HC(6' or 3')), 11.96 (s, 1H, SH). ^{13}C-NMR: 21.1 (CH_3), 59.0 (CH), 73.8 (CH_2), 120.1/12.2/130.2/131.0/132.9/154.2 (Ph), 167.3 (C=N). MS (CI): 194(100, M^++1), 193(12). TLC (hexane/ EtOAc 3:1): R_f = 0.23. The product **9a** slowly decomposes upon standing at 4 °C, forming insoluble polymers. Experiments with this ligand were carried out with freshly prepared samples that had been stored at –20 °C for not more than one week.

(4S)-4,5-Dihydro-2-(2'-mercaptophenyl)-4-isopropyloxazole (**9b**). The product was recrystallized from EtOH/petroleum ether (45% yield, yellow needles, m.p. 119-120 °C). $[\alpha]_D$ = +124 (c = 0.93, $CHCl_3$). IR: 2360w, 1624s, 1528s, 1497s, 1412s, 1371m, 1288m, 1266m, 1058s, 938s, 742s. ^{1}H-NMR: 1.01 (d, J = 6.7, 3H, CH_3), 1.08 (d, J = 6.7, 3H, CH_3), 1.82-1.96 (m, 1H, $HCMe_2$), 4.22-4.33 (m, 2H, $H_2C(5)$), 4.57-4.63 (m, 1H, HC(4)), 6.94-6.99 (m, 1H, HC(5' or 4')), 7.16-7.22 (m, 1H, HC(4' or 5')), 7.57 (d, J = 8.0, 1H, HC(3')), 7.78 (dd, J = 1.3, 8.1, 1H, HC(6')), 13.25 (s, 1H, SH). ^{13}C-NMR: 19.1 (CH_3), 19.2 (CH_3), 33.3 ($CHMe_2$), 69.5 (HC(4)), 71.5 ($H_2C(5)$), 120.1/122.3/130.8/131.7/134.3/153.2 (Ph), 168.7 (C=N). MS (EI): 221(19, M^+), 220(100), 152(26). TLC (hexane/EtOAc 6:1): R_f = 0.24. Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.34; H, 7.01; N, 6.31.

(4S)-4,5-Dihydro-2-(2'-mercaptophenyl)-4-tert-butyloxazole (**9c**). Yellow solid, 61% yield, m.p. 65-66 °C, $[\alpha]_D$ = +153 (c = 1.08, $CHCl_3$). IR: 2400w, 1634s, 1560w, 1481s, 1354m, 1244m, 1212m, 1048s, 969m, 906m. ^{1}H-NMR: 1.00 (s, 9H, *t*-Bu), 4.24 (dd, J = 7.2, 10.0, 1H, HC(5)), 4.41 (dd, J = 7.2, 9.1, 1H, HC(5)), 4.54 (dd, J = 9.1, 10.0, 1H, HC(4)), 6.93-6.98 (m, 1H, HC(5' or 4')), 7.17-7.2 (m, 1H, HC(4' or 5')), 7.59 (d, J = 8.1, 1H, HC(3')), 7.78 (dd, J = 1.5, 8.1, 1H, HC(6')). ^{13}C-NMR: 25.5 (CH_3), 33.7 (C), 69.1 (CH), 72.0 (CH_2), 119.1/121.5/128.2/130.1/131.2/134.0 (Ph), 168.5 (C=N). MS (CI): 236(100, M^++1), 235(10). TLC (hexane/EtOAc 12:1): R_f = 0.15. Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; 5.95. Found C, 66.19; H, 7.33; N, 5.90.

(4S)-4,5-Dihydro-2-(2'-mercaptophenyl)-4-benzyloxazole (**9d**). Yellow oil, 48% yield. $[\alpha]_D$ = +128 (c = 0.7, $CHCl_3$). IR: 2400w, 1522s, 1423s, 1046s, 928s. ^{1}H-NMR: 2.87 (dd, J = 7.4, 13.8, 1H, CH_2Ph), 3.14 (dd, J = 6.3, 13.8, 1H, CH_2Ph), 4.19 (dd, J = 7.5, 8.4, 1H, HC(5)), 4.44 (dd, J = 8.4, 9.0, 1H, HC(5)), 4.64-4.73 (m, 1H, HC(4)), 6.98-7.04 (m, 1H, HC(5' or 4')), 7.18-7.35 (m, 6H, Ph), 7.46 (d, J = 8.1, 1H, HC(3')), 7.80 (dd, J = 1.5, 8.1, 1H, HC(6')). ^{13}C-NMR: 41.5 ($\underline{C}H_2Ph$), 65.9 (HC(4)), 71.3 ($H_2C(5)$), 122.6/126.8/128.4/128.6/129.1/129.3/130.3/130.9/131.9/136.9 (Ph), 166.5 (C=N). MS (CI): 270(100, M^++1), 178 (53). TLC (hexane/EtOAc 10:1): R_f = 0.16.

(4S,5S)-4,5-Dihydro-2-(2'-mercaptophenyl)-4-[{(tert-butyl)dimethylsilyloxy}methyl]-5-phenyloxazole (**9e**). Yellow oil, 57% yield. $[\alpha]_D$ = +29.3 (c = 0.9, $CHCl_3$). IR: 2359w, 1646s, 1502m, 1471s, 1323m, 1256s, 1117s, 1046m, 959m, 835s. ^{1}H-NMR: 0.08 (s, 3H, CH_3-Si), 0.19 (s, 3H, CH_3-Si), 0.89 (s, 9H, *t*-Bu), 3.83 (dd, J = 6.4, 10.3, 1H, CH_2), 4.01 (dd, J = 4.0, 10.3, 1H, CH_2), 4.38 (m, 1H, HC(4)), 5.56 (d, J = 6.3, HC(5)), 7.08 (m, 1H, HC(5' or 4')), 7.25 (m, 1H, HC(4' or 5')), 7.28-7.39 (m, 5H, Ph), 7.45 (d, J = 8.1, 1H, HC(3')), 7.97 (d, J = 8.0, HC(6')), 10.07 (s, 1H, SH). ^{13}C-NMR: –5.3 (CH_3-Si), 18.2 (C-Si), 25.8 ($\underline{C}H_3$-C), 64.7 (CH_2), 75.3 (HC(4)), 82.6 (HC(5)), 123.2/125.6/128.3/128.5/128.6/128.8/130.6/130.9/131.2/140.2 (Ph), 165.7 (C=N). MS (FAB): 400(14), 399(46, M^+). TLC (hexane/EtOAc 8:1): R_f = 0.51. Anal. Calcd for $C_{22}H_{29}NO_2SSi$: C, 66.12; H, 7.31; N, 3.50. Found: C, 65.84; H, 7.28; N, 3.41.

Synthesis of the (2-Mercapto-3,5-dimethylphenyl)oxazoline Ligand 13. *Oxazoline Formation.*[26] To a solution of 3.00 g (20 mmol) of 3,5-dimethylbenzoic acid in 40 ml of CH_2Cl_2, 3.17 g (25 mmol) of oxalyl choride was slowly added at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 15 h. Aqueous ammonia (20 ml of a 25% solution) was added at 0 °C over 20 min. The resulting mixture was poured into 100 ml of H_2O and extracted with 3 x 100 ml of Et_2O. Drying over Na_2SO_4 and concentration *in vacuo* afforded 3,5-dimethylbenzamide (2.84 g, 95%) as a white solid (m.p. 134-135 °C).

3,5-Dimethylbenzamide (2.5 g, 16.8 mmol) was added to a solution of 3.18 g (16.8 mmol) of triethyloxonium tetrafluoroborate in 150 ml of anhydrous dichloroethane. After stirring for 20 h at room temperature, 1.9 g (18.5 mmol) of L-valinol was added. The mixture was refluxed for 24 h, diluted with 150 ml of CH_2Cl_2, and washed with saturated aqueous Na_2CO_3, H_2O, and saturated NaCl solution. Drying over Na_2SO_4, removal of the solvent *in vacuo* followed by flash column chromatography with hexane/EtOAc (6:1) afforded 3.34 g (91%) of (4*S*)-4,5-dihydro-2-(3',5'-dimethylphenyl)-4-isopropyloxazole as a colorless oil. $[\alpha]_D$ = –74 (c = 1.5, $CHCl_3$). IR: 1640s, 1590s, 1455s, 1372s, 1345s, 1312m, 1255m, 1200s, 985s, 910s, 848s. ^{1}H-NMR: 0.92 (d, J = 6.7, 3H, CH-$\underline{C}H_3$), 1.02 (d, J = 6.7, 3H, CH-$\underline{C}H_3$), 1.75-1.92 (m, 1H, CH), 2.33 (s, 6H, $PhCH_3$), 4.03-4.15(m, 2H, $H_2C(5)$), 4.30-4.42 (m, 1H, HC(4)), 7.08 (s, 1H, HC(4')), 7.58 (s, 2H, HC(2'), HC(6')). ^{13}C-NMR: 17.9 (CH_3), 18.9 (CH_3), 21.1 (CH_3), 32.7 ($\underline{C}HMe_2$), 69.8 (CH_2), 72.5 (HC(4)), 125.9/127.6/132.7/137.8 (Ph), 163.6 (C=N). MS (CI): 219(16), 218(100, M^++1), 174(16). TLC (hexane/EtOAc 6:1): R_f = 0.61. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.42; H, 8.76; N, 6.45. Found: C, 77.40; H, 8.72; N, 6.35.

(4S)-4,5-Dihydro-2-(2'-mercapto-3',5'-dimethylphenyl)-4-isopropyloxazole (**13**). To a solution of 1.10 g (5 mmol) of (4*S*)-4,5-dihydro-2-(3',5'-dimethylphenyl)-4-isopropyloxazole in 25 ml of THF, 3.5 ml (5.5 mmol) of *n*-BuLi (1.6 M in hexane) was added dropwise at -45 °C. The resulting solution was stirred at this temperature for 2 h and transferred through a cannula into a suspension of 160 mg (5 mmol) of sublimated sulfur in 20 ml of THF at -45 °C. The mixture was gradually warmed up to room temperature and stirred for an additional 1 h. Addition of 2 M aqueous HCl (2.75 ml, 5.5 mmol), subsequent extraction with Et_2O, washing with water, and flash column chromatography (hexane/EtOAc 6:1) afforded (150 mg, 12%) of **13** as a yellow crystaline solid (m.p. 108 °C). $[\alpha]_D$ = +47 (c = 1.1, $CHCl_3$). IR: 2422w, 1622s, 1527m, 1455s, 1438s, 1361m, 1266m, 1061m, 1000s, 966s. ^{1}H-NMR: 0.99 (d, J = 6.7, 3H, $\underline{C}H_3$-CH), 1.07 (d, J = 6.7, 3H, $\underline{C}H_3$-CH), 1.82-1.92 (m, 1H, $\underline{C}HMe_2$), 2.26 (s, 3H, Ph-CH_3), 2.40 (s, 3H, Ph-CH_3), 4.18-4.27 (m, 2H, $H_2C(5)$), 4.42-4.52 (m, 1H, HC(4)), 7.17 (d, J = 1.4, 1H, HC(4')), 7.58 (s, 1H, HC(6')), 12.76 (s, 1H, SH). ^{13}C-NMR: 18.6 (CH_3), 18.8 (CH_3), 20.6 (CH_3), 21.9 (CH_3), 32.7 (CH), 70.1 (HC(4)), 70.4 ($H_2C(5)$),

128.2(double intensity)/131.0/133.7(double intensity)/138.2 (Ph), 167.2 (C=N). MS (EI): 249(81, M^+), 206(19), 163(100). TLC (hexane/EtOAc 6:1): R_f = 0.32. Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68; N, 5.62. Found: C, 67.36; H, 7.71; N, 5.57.

[(4'*S*)-{2-[2'-(4',5'-Dihydro-4'-isopropyloxazolyl)]thiophenolato}copper(I)] Complex [(12b)$_n$]. A solution of 110.5 mg (0.5 mmol) of ligand **9b** in 20 ml of THF was treated with 0.35 ml (0.55 mmol) of *n*-BuLi (1.6 M in hexane) at -78 °C. After stirring at -78 °C for 10 min, the solution was transferred through a cannula into a suspension of 95 mg (0.5 mmol) of CuI in 20 ml of THF at -78 °C. The mixture was warmed up to -20 °C and stirred at this temperature for 30 min to form a homogeneous solution. After removal of the solvent *in vacuo* at room temperature, the remaining solid was recrystallized from CH_2Cl_2/CH_3OH to afford yellow crystals of compex **12a** (m.p. 225-230 °C (dec.); 120 mg; 84%). ^{1}H-NMR: 0.34 (d, J = 6.9, 3H, CH_3), 0.50 (d, J = 6.7, 3H, CH_3), 1.46-1.51 (m, 1H, C<u>H</u>Me$_2$), 3.84-3.90 (m, 1H, HC(4')), 4.10 (d, J = 7.5, 2H, CH_2), 7.06 (t, J = ca. 7.5, 1H, HC(4 or 5)), 7.21 (t, J = ca. 7.3, 1H, HC(5 or 4)), 7.86 (d, J = 7.6, 1H, HC(6 or 3)), 7.92 (d, J = 7.8, 1H, HC(3 or 6)). ^{13}C-NMR: 14.3 (CH_3), 18.6 (CH_3), 30.6 (<u>C</u>HMe$_2$), 65.6 (HC(4')), 71.8 (CH_2), 123.3/124.2/130.1/ 130.9/136.6/146.5 (Ph), 164.7 (C=N). MS (FAB): 1203(6), 1202(12), 1201(30), 1200(29), 1199(54), 1198(30), 1197(51), 1195(20, {**12b**}$_4$ + Cu^+ / ^{63}Cu); 919(4), 918(18), 917(17), 916(48), 915(25), 914(61), 913(8), 912(32, {**12b**}$_3$ + Cu^+/ ^{63}Cu); 856(7), 855(18), 854(32), 853(62), 852(58), 851(100), 850(41), 849(61, {**12b**}$_3$ / ^{63}Cu); 635(5), 634(6), 633(27), 632(15), 631(53), 630(11), 629(40, {**12b**}$_2$ + Cu^+ / ^{63}Cu); 571(7), 570(30), 569(31), 568(100), 567(36), 566(98, {**12b**}$_2$ / ^{63}Cu). Anal. Calcd for $C_{12}H_{14}NOSCu$: C, 50.79; H, 4.94; N, 4.94. Found: C, 50.60; H, 4.95; N, 4.85.

Copper-Catalyzed 1,4-Addition. *General procedure: 3-Butylcycloheptenone.*. To a solution of 26.5 mg (0.12 mmol) of ligand **9b** in 5 ml of THF, 75 µl (0.12 mmol) of *n*-BuLi (1.6 M in hexane) was added dropwise at -78 °C. After stirring at -78 °C for 10 min, the solution was transferred through a cannula to the reaction flask containing a suspension of 19 mg (0.10 mmol) of CuI in 5 ml of THF at -78 °C. The mixture was warmed to -20 °C and stirred at this temperature for 30 min. The resulting greenish yellow homogeneous solution was cooled to -78 °C. Then 0.35 ml (2.0 mmol) of HMPA was added and stirring was continued for 5 min until all HMPA had dissoved. After addition of 110 mg (1.0 mmol) of cycloheptenone, 2.0 ml (1.0 mmol) of *n*-BuMgCl (0.5 M in THF) was added at -78 °C by a syringe pump over a period of 2 h. The resulting orange solution was stirred at that temperature for an additional 2 h. After quenching with 5 ml of saturated aqueous NH_4Cl solution, the mixture was warmed to room temperature and extracted with 30 ml of Et_2O. The ether phase was washed twice with 1 N HCl and twice with water. Flash column chromatography with pentane/Et_2O (6:1) gave 85 mg (50%) of (*R*)-3-butylcycloheptanone (83% ee). $[\alpha]_D$ = +44.2 (c = 2.3, $CHCl_3$). IR: 1691s. ^{1}H-NMR: 0.98 (t, J = 6.7, 3H, CH_3), 1.20-1.95 (m, 13H, CH + 6 CH_2), 2.33-2.50 (m, 4H), 2 CH_2).[27] ^{13}C-NMR: 14.0 (CH_3), 22.7/24.3/28.5/29.1/36.8/36.9/43.8/49.9 (CH_2), 35.9 (CH), 214.5 (C=O). The enantiomeric purity was determined by ^{13}C-NMR analysis after ketalization with (*R,R*)-(-)-2,3-butanediol.[23]

(R)-3-Isopropylcycloheptanone. $[\alpha]_D$ = + 61.4 (c = 1.92, $CHCl_3$), 87% ee by ^{13}C-NMR.[23] IR ($CHCl_3$): 1691s. ^{1}H-NMR: 0.86 (d, J = 6.8, 3H, CH_3), 0.88 (d, J = 6.7, 3H, CH_3), 1.22-2.05 (m, 8H, 2CH + 3CH_2), 2.31-2.51 (m, 4H, 2CH_2). ^{13}C-NMR: 18.8 (CH_3), 19.2 (CH_3), 24.6/29.1/33.5/43.7/47.0 (CH_2), 33.6/41.8 (CH), 214.9 (C=O).

(R)-3-Butylcyclohexanone. $[\alpha]_D$ = + 9.4 (c = 2.78, $CHCl_3$), 60% ee by ^{13}C-NMR.[23] IR ($CHCl_3$): 1705s. ^{1}H-NMR: 0.92 (t, J = 7.0, 3H, CH_3), 1.25-2.55 (m, 15H, CH + 7CH_2). ^{13}C-NMR: 13.9 (CH_3), 22.6/25.2/ 28.7/31.2/36.2/41.4/48.1 (CH_2), 38.9 (CH), 211.9 (C=O).

(R)-3-Isopropylcyclohexanone. $[\alpha]_D$ = + 13.6 (c = 1.92, $CHCl_3$), 72% ee by ^{13}C-NMR.[23] IR ($CHCl_3$): 1702s. ^{1}H-NMR: 0.90 (d, J = 6.5, 3H, CH_3), 0.91 (d, J = 6.6, 3H, CH_3), 1.28-2.42 (m, 10H, 2CH + 4CH_2). ^{13}C-NMR: 19.2 (CH_3), 19.5 (CH_3), 25.4/28.2/41.4/45.2 (CH_2), 32.4/45.3 (CH), 212.5 (C=O).

(R)-3-Butylcyclopentanone. $[\alpha]_D$ = + 22.2 (c = 1.93, $CHCl_3$), 27% ee by ^{13}C-NMR.[23] IR ($CHCl_3$): 1731s. ^1H-NMR: 0.91 (t, J = 6.8, 3H, CH_3), 1.25-2.45 (m, 13H, CH + $6CH_2$). ^{13}C-NMR: 13.9 (CH_3), 22.7/29.5/30.0/35.3/38.4/45.2 (CH_2), 37.1 (CH), 219.9 (C=O).

(R)-3-Isopropylcyclopentanone. $[\alpha]_D$ = + 47.1 (c = 2.35, $CHCl_3$), 37% ee by ^{13}C-NMR.[23] IR ($CHCl_3$): 1734s. ^1H-NMR: 0.94 (d, J = 6.7, 3H, CH_3), 0.95 (d, J = 6.7, 3H, CH_3), 1.40-2.45 (m, 8H, 2CH + $3CH_2$). ^{13}C-NMR: 20.4 (CH_3), 21.3 (CH_3), 27.8/39.2/43.7 (CH_2), 33.6/44.7 (CH), 219.6 (C=O).

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