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# Enantioselective addition of methyllithium to a prochiral imine—the substrate in the Pomeranz–Fritsch–Bobbitt synthesis of tetrahydroisoquinoline derivatives mediated by chiral monooxazolines

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**Abstract**—A series of chiral monooxazoline ligands **7**–**24** with substituents at C-2 and C-4, differing in electronic and steric properties, has been synthesized from (+)-thiomicamine **6**. The effect of the oxazoline structure on the course of addition of methyllithium to imine **1** has been studied. The addition product, amine **3**, which is the key intermediate in the Pomeranz–Fritsch–Bobbitt synthesis of tetrahydroisoquinoline derivatives, has been obtained in high yield (92%) and with up to 76% ee.


## 1. Introduction

Asymmetric addition of carbon nucleophiles to the carbon–nitrogen double bond of imines with the introduction of a stereogenic center at the α-position has provided rapid access to enantiomerically pure or enriched amines. The stereoselectivity of this process has been accomplished either by diastereoselective synthesis, requiring the covalent attachment of a chiral auxiliary to substrates, or in reactions mediated by external chiral ligands. The literature of the past decade, concerning diastereoselective and enantioselective nucleophilic additions to imines and their derivatives, has been reviewed in several comprehensive articles.[1–5]

The synthetic approach, involving reactions of prostereogenic imines with organometallic reagents, carried out in the presence of stoichiometric or catalytic amounts of external chiral ligands, has recently gained growing attention and successfully competes with the more common diastereoselective synthesis.[6] In this regard, the design and synthesis of new and efficient chiral ligands plays a crucial role. For enantioselective addition of organometallic reagents to the C=N bond, a variety of chiral ligands, most of which contained nitrogen and/or oxygen functional groups, such as (−)-sparteine,[7,8] bisoxazolines,[8–10] aminoethers,[11–13] and diol ethers,[13] have been recently developed. A number of monooxazolines derived from (1*S*,2*S*)-2-amino-1-aryl-1,3-propandiols have been synthesized and tested as ligands in enantioselective additions of organometallic reagents to imines, cyclic[14] and Schiff base-type.[15]

## 2. Results and discussion

One aspect of our interest in the asymmetric synthesis of isoquinoline alkaloids[16] has been directed toward the enantioselective modification of the Pomeranz–Fritsch–Bobbitt synthesis.[15] This approach, realised for the first time in this manner, afforded enantiomerically enriched (*S*)-salsolidine **4** and (*S*)-carnegine **5** (Scheme 1).

The modification involved addition of methyl organometallic reagents to the 'Pomeranz–Fritsch' imine **1** carried out in the presence of oxazolines **2** (R = $SCH_3$, H; $R_2$ = H, $CH_3$) derived from (+)-thiomicamine **6**, and its desulfurated analogue, (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanodiol, used as external chiral ligands (Fig. 1). The resulting amine **3** was obtained in high yield but with only 49% ee. To improve the enantioselectivity

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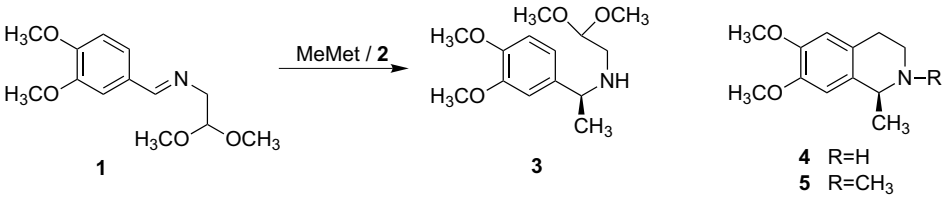


**Scheme 1.**

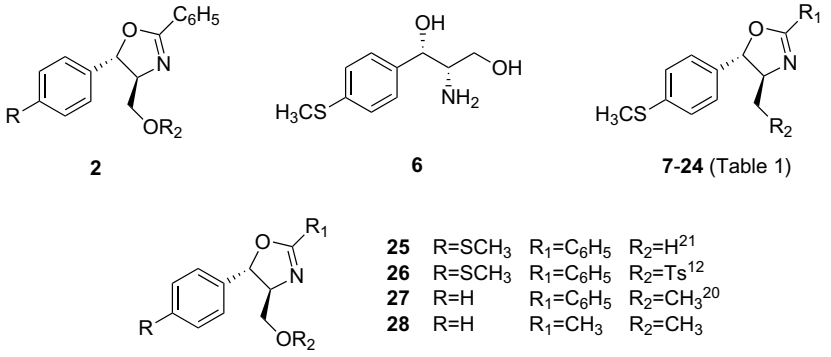


**Figure 1.**

of the addition step, crucial for the synthesis, we have undertaken a further study focused mainly on structural modifications of ligands.

Chiral oxazolines were chosen as ligands in this reaction not only because of the well documented efficiency of monooxazolines[17] and bisoxazolines[18] in introducing chirality in many asymmetric reactions, in particular as most promising in additions to imines, but also because they were prepared from (1*S*,2*S*)-2-amino-1-aryl-1,3-propandiols, industrial waste products.

In continuation of this project, we have synthesized from (+)-thiomicamine **6** several new oxazolines **7**–**24**, with $R_1$ and $R_2$ substituents differing in steric and electronic properties (Table 1). Since hydroxy oxazolines of type **7**–**11** have been found[15] to give poor asymmetric induction in these additions *O*-protected derivatives, **14**–**24**, along with two known others, **27**[15] and commercially available **28**, were tested for their ability to control the steric course of the addition of methyllithium to imine **1**, in the hope that amine **3** could be produced with higher enantiomeric purity (Table 2). Imine **1** was chosen as the sole object of our study not only because the resulting chiral amine **3** could be used as substrate in asymmetric synthesis of tetrahydroisoquinoline derivatives according to the Pomeranz–Fritsch–Bobbitt method, but because the addition of organometallic reagents to

**Table 1.** Oxazolines **7**–**24** synthesized from (1*S*,2*S*)-(+)-thiomicamine **6**

| Oxazoline no. | $R_1$ | $R_2$ | *Y* (%) | Mp (°C)/solvent* | $[\alpha]_D$ | HRMS ($M^+$) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Found | Calcd |
| **7** | *o*-$C_6H_4OH$ | OH | 60 | 104–107 (a) | +91.9 (*c* 0.47, MeOH) | 315.09524 | 315.09293 $C_{17}H_{17}NO_3S$ |
| **8** | *m*-$C_6H_4Me$ | OH | 71 | 162–164 (b) | +61.4 (*c* 0.50, $CH_2Cl_2$) | 313.11532 | 313.11365 $C_{18}H_{19}NO_2S$ |
| **9** | Me | OH | 63 | 109–111 (c) | −147.9 (*c* 1.03, $CH_2Cl_2$) | 237.08156 | 237.08235 $C_{12}H_{15}NO_2S$ |
| **10** | Et | OH | 28 | 127–129 (d) | −121.7 (*c* 1.02, $CH_2Cl_2$) | 251.09823 | 251.09801 $C_{13}H_{17}NO_2S$ |
| **11** | *i*-Pr | OH | 7 | 81.5–84 (c) | −92.5 (*c* 1.02, $CH_2Cl_2$) | 265.11303 | 265.11365 $C_{14}H_{19}NO_2S$ |
| **12** | Ph | OMs | 89 | 103–105 (c) | +29.8 (*c* 0.99, $CHCl_3$) | 377.07375 | 377.07556 $C_{18}H_{19}NO_4S_2$ |
| **13** | Ph | $SCOCH_3$ | 72 | 123–126 (e) | +79.3 (*c* 1.00, $CHCl_3$) | 357.08539 | 357.08572 $C_{19}H_{19}NO_2S_2$ |
| **14** | *o*-$C_6H_4OMe$ | OMe | 94 | Oil | +50.6 (*c* 0.89, $CH_2Cl_2$) | 343.12358 | 343.12421 $C_{19}H_{21}NO_3S$ |
| **15** | *m*-$C_6H_4Me$ | OMe | 95 | 69–72 (f) | +66.1 (*c* 1.03, $CH_2Cl_2$) | 327.12700 | 327.12930 $C_{19}H_{21}NO_2S$ |
| **16** | Me | OMe | 96 | Oil | −119.5 (*c* 0.98, $CH_2Cl_2$) | 251.09791 | 251.09801 $C_{13}H_{17}NO_2S$ |
| **17** | Et | OMe | 95 | Oil | −102.7 (*c* 1.08, $CH_2Cl_2$) | 265.11431 | 265.11365 $C_{14}H_{19}NO_2S$ |
| **18** | *i*-Pr | OMe | 94 | Oil | −87.1 (*c* 0.99, $CH_2Cl_2$) | 279.12876 | 279.12930 $C_{15}H_{21}NO_2S$ |
| **19** | Me | OTs | 70 | 116.5–119.5 (g) | −127.9 (*c* 0.88, MeOH) | 391.09125 | 391.09122 $C_{19}H_{21}NO_4S_2$ |
| **20** | Me | $Si(Me)_2t$-Bu | 99 | Oil | −77.7 (*c* 1.10, $CH_2Cl_2$) | 351.17058 | 351.16882 $C_{18}H_{29}NO_2SSi$ |
| **21** | Ph | $Si(Me)_2t$-Bu | 98 | Oil | +55.4 (*c* 0.57, $CH_2Cl_2$) | 413.18516 | 413.18448 $C_{23}H_{31}NO_2SSi$ |
| **22** | Ph | OPh | 40 | 123–125 (h) | −22.0 (*c* 1.01, $CHCl_3$) | 375.12686 | 375.12930 $C_{23}H_{21}NO_2S$ |
| **23** | Ph | SMe | 48 | 122–125 (c) | +130.1 (*c* 0.98, $CH_2Cl_2$) | 329.08941 | 329.09082 $C_{18}H_{19}NOS_2$ |
| **24** | Ph | STol | 68 | 78–80 (f) | +142.1 (*c* 0.99, MeOH) | 405.12105 | 405.12210 $C_{24}H_{23}NOS_2$ |

* Crystallization solvents: (a) $CCl_4$, (b) $CH_2Cl_2$, (c) $CH_2Cl_2$/hexane, (d) $CH_2Cl_2$/*i*-$Pr_2O$, (e) $CHCl_3$, (f) $Et_2O$, (g) MeOH, (h) EtOH/*i*-$Pr_2O$.

**Table 2.** Addition of methyllithium to imine **1** in the presence of ligands **2** (R = $SCH_3$), **14**–**24**, and **26**–**28**[a]

| Entry | Oxazolines No. | $R_1$ | $R_2$ | Addition product **3**[b] 2.6 equiv of ligand $Y$ (%) | 2.6 equiv of ligand Ee (%)[c] | 0.5 equiv of ligand $Y$ (%) | 0.5 equiv of ligand Ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **2** | Ph | OMe | 92 | 49 | 44 | 22 |
| 2 | **27** | Ph | OMe | 89 | 42 | — | — |
| 3 | **14** | *o*-$C_6H_4OMe$ | OMe | 59 | 8[d] | — | — |
| 4 | **15** | *m*-$C_6H_4Me$ | OMe | 88 | 20 | 84 | 14 |
| 5 | **16** | Me | OMe | 92 | 76 | 90 | 65 |
| 6 | **28** | Me | OMe | 89 | 76 | 82 | 67 |
| 7 | **17** | Et | OMe | 84 | 52 | 90 | 41 |
| 8 | **18** | *i*-Pr | OMe | 57 | 16 | 83 | 6 |
| 9 | **26** | Ph | OTs | 72 | 15 | 74 | 5 |
| 10 | **19** | Me | OTs | 75 | 14 | 76 | 11 |
| 11 | **20** | Me | $OSi(Me)_2$-*t*-Bu | 80 | 27 | — | — |
| 12 | **21** | Ph | $OSi(Me)_2$-*t*-Bu | 77 | 15 | — | — |
| 13 | **22** | Ph | OPh | 48 | 30 | — | — |
| 14 | **23** | Ph | SMe | 58 | 6 | — | — |
| 15 | **24** | Ph | STol | 50 | 2 | — | — |

[a] Reaction conditions: toluene, MeLi (2.5 equiv), $T = -65\,^{\circ}C$, preliminary interaction of imine **1** with ligand 1.0 h, reaction time 2.5 h.
[b] Absolute configuration of amine **3** was determined to be (*S*) by conversion of (−)-**3** to (*S*)-(−)-salsolidine **4**.[15]
[c] Established by HPLC with Chiracel OD-H column.
[d] (*R*)-configuration of the major enantiomer (HPLC).

imines strongly depends on the structure of substrates (imine and nucleophile) as well as on the ligand. This approach allowed the evaluation of the effectiveness of the ligands employed (Table 2).

Enantiomerically pure oxazoline ligands **14**–**24**, listed in Table 1, have been prepared by the reaction of (+)-thiomicamine **6** with the appropriate nitrile according to the known procedure,[19] via the 4-hydroxymethyl precursors **7**–**11** or esters **12**, **13**. Oxazoline **9** with the methyl substituent at C-2 has been prepared by the orthoester method.[20] *O*-Methylation of alcohols **7**–**11** to give methoxy derivatives **14**–**18**, proceeded in high yield when treated with $NaH/CH_3I$ reagents in DMF or THF. Sulfonyl esters **12** and **19** have been prepared by reacting oxazolines **25** and **9**, respectively, with mesyl chloride in THF and tosyl chloride in methylene chloride, in the presence of triethylamine. *O*-Silylated derivatives **20** and **21** have been obtained from alcohols **9** and **25**, respectively, in the reaction with TBDMSCl/imidazole/DMF reagents system. A three-step procedure was needed for the synthesis of *O*-phenyl **22** and *S*-tolyl **24** oxazolines in which intermediate sulfonates **26** and **12** were reacted with sodium phenolate and sodium thiophenolate in DMF, respectively. Oxazoline **23** with methylthiomethyl group at C-4 was prepared from sulfonate **12** via thioacetate **13** in a sequence of reactions involving substitution of mesylate with potassium thioacetate and in situ hydrolysis/methylation of the latter.

The results of the addition reactions of methyllithium to *E*-imine **1**[15] carried out in the presence of (4*S*,5*S*)-oxazolines **2** (R = $SCH_3$), **14**–**24**, and **26**–**28** affording amine **3**, are shown in the Table 2.

The reaction conditions, that is: toluene as the solvent, 2.5 equiv of methyllithium and 2.6 equiv of the ligand, followed those established previously,[8,15,22] while the temperature was kept at −65 °C. In the subsequent reactions, the amount of the ligand was successively reduced to 0.5 equiv, but in all cases the enantioselectivity was higher with large excess (2.6 equiv) of the ligand, noticed also by others[8,22] (Table 2, column 6 vs column 8). It should be added that in the absence of ligands no addition to imine **3** occurred, under these reaction conditions. Unchanged ligands could be recovered from the crude reaction products by column chromatography.

The best results, in terms of the yield (92% and 89%) and enantioselectivity (76% ee), were obtained in the reactions carried out in the presence of oxazolines **16** and **28**, substituted with methyl groups at the C-2 and the C-4 side chain (entries 5, 6). In general, oxazolines with methyl group at the C-2, **16**, **20**, **28**, produced amine **3** with a higher degree of enantioselectivity then 2-phenyl analogues, **2**, **21**, **27**, as evidenced by comparison of entries 5, 11, 6 with entries 1, 12, 2. On the other hand, with the increasing size of the C-2 substituent the ee of amine **3** decreased. In the aromatic series, introduction of *o*-methoxy and *m*-methyl group into the phenyl ring, as in compounds **14** and **15**, resulted in a decrease of ee proportional to the size and site of the substitution, when compared with the reaction using **2** (entries 1, 3, 4). Going from oxazoline **16** with methyl substituent at C-2 to **17** (C-2 ethyl) and **18** (C-2 *iso*-propyl), the ee dropped dramatically in the same direction (entries 5, 7, 8).

The substituent at the C-4 side chain is important for the steric course of this process as well. Introduction of groups bulkier then methyl onto the oxygen, as in ligands **19**, **26**, **20**, **21** or phenyl in **22**, resulted in reduction of ee significantly (entries 9–13), while sulfur analogues **23** and **24** led to a nearly racemic product (entries 14, 15).

All the (4*S*,5*S*)-ligands tested (but one, **14**, entry 3) have produced amine **3** with (*S*) configuration as the domi-

nant enantiomer. The absolute configuration was established by comparison (HPLC, Chiracel OD-H column) with a sample of (*S*)-(−)-**3** of known configuration.[15] Formation of the (*R*) isomer, albeit with very poor selectivity, could be associated with the presence of a third coordinating site[22] in **14** at the C-2 aromatic substituent.

## 3. Conclusion

A series of homochiral monooxazoline ligands **7**–**24** derived from (+)-thiomicamine **6** has been synthesized and the influence of oxazoline structure on the yield and the enantioselectivity of addition of methyllithium to prochiral imine **1** has been studied. Since the addition of organometallic reagents to imines is a substrate specific process, the maintenance of standard reagents and conditions in these experiments is an important factor. Thus, by testing oxazolines with substituents at C-2 and C-4, of different properties, it was possible to show that both types of effects, electronic and steric play important roles in this process (Table 2). The addition product, amine **3**, which is a key substrate in the enantioselective Pomeranz–Fritsch–Bobbitt synthesis of tetrahydroisoquinoline derivatives, has been obtained in high yield (up to 92%) and with enantiomeric excess reaching 76%, when ligands **16** or **28**, with methyl substituents, were applied to control this process.

## 4. Experimental

### 4.1. General

Melting points: determined on a Koffler block and are not corrected. IR spectra: Perkin–Elmer 180 in KBr pellets and films. NMR spectra: Varian Gemini 300, in $CDCl_3$ and DMSO-$d_6$, with TMS as internal standard. Mass spectra (EI): Joel D-100, 75 eV. Optical rotations: Perkin–Elmer polarimeter 243B at 20 °C. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography and Merck DC-Alufolien Kieselgel $60_{254}$ for TLC. Analytical HPLC: Waters HPLC system with Mallinkrodt-Baker Chiracel OD-H column. (+)-Thiomicamine was purchased from the Aldrich Chemical Co. and used as received. MeLi was purchased from the Acros Organics (1.6 M solution in diethyl ether, low chloride).

### 4.2. Synthesis of oxazoline ligands

**4.2.1. Synthesis 4-hydroxymethyl-2-oxazolines.[19] General procedure.** To a suspension of (1*S*,2*S*)-(+)-thiomicamine **6** (4.26 g, 20 mmol) and potassium carbonate (0.43 g) in a mixture of ethylene glycol (6.4 mL) and glycerol (3.5 mL) was added excess nitrile (30–50 mmol). The mixture was heated at 105–125 °C with stirring under an argon atmosphere until no more oxazoline was produced (TLC, 7.5–35 h). After cooling to ambient temperature water was added to the mixture and the product was collected by filtration or extracted with $CH_2Cl_2$ or $CHCl_3$/*i*-PrOH: 3/1 until the Dragendorff test was negative. In the latter case the combined organic extracts were dried and worked-up in the usual way.

**4.2.1.1. (4*S*,5*S*)-4-Hydroxymethyl-2-(2-hydroxyphenyl)-5-[4-(methylthio)phenyl]-2-oxazoline 7.** The reaction with 2-hydroxybenzonitrile (3.6 g, 30 mmol) was carried at 120 °C for 35 h. IR (KBr), $\nu$ ($cm^{-1}$): 3225 (OH), 1640 (C=N); $^1H$ NMR ($CDCl_3$ + $D_2O$) $\delta$: 2.49 (s, 3H, $SCH_3$), 3.79 (dd, $J$ = 11.8, 3.8 Hz, 1H, C*H*HOH), 3.99 (dd, $J$ = 11.8, 3.8 Hz, 1H, CH*H*OH), 4.31 (td, $J$ = 7.4, 3.8 Hz, 1H, H-4), 4.80 (br s, 1H, HOD), 5.50 (d, $J$ = 7.4 Hz, 1H, H-5), 6.87–6.93 (m, 1H, ArH), 7.04 (dd, $J$ = 8.2, 0.8 Hz, 1H, ArH), 7.19–7.44 (m, 4H, ArH), 7.73 (dd, $J$ = 8.0, 1.6 Hz, 1H, ArH); EIMS *m*/*z* (%): 315 (M+, 47), 195 (41), 178 (12), 165 (48), 163 (7), 150 (42), 146 (11), 137 (17), 121 (100), 117 (18), 92 (13), 65 (15).

**4.2.1.2. (4*S*,5*S*)-4-Hydroxymethyl-5-[4-(methylthio)-phenyl]-2-(3-tolyl)-2-oxazoline 8.** The reaction with *m*-tolunitrile (4.8 mL, 40 mmol) was carried at 125 °C for 18 h. IR (KBr), $\nu$ ($cm^{-1}$): 3204 (OH), 1644 (C=N); $^1H$ NMR ($CDCl_3$ + $D_2O$) $\delta$: 2.35 (s, 3H, $PhCH_3$), 2.48 (s, 3H, $SCH_3$), 3.75 (dd, $J$ = 11.8, 3.8 Hz, 1H, C*H*HOH), 4.09 (dd, $J$ = 11.8, 3.3 Hz, 1H, CH*H*OH), 4.21 (td, $J$ = 8.0, 3.5 Hz, 1H, H-4), 4.73 (br s, 1H, HOD), 5.52 (d, $J$ = 8.0 Hz, 1H, H-5), 7.22–7.34 (m, 6H, ArH), 7.71 (s, 2H, ArH); EIMS *m*/*z* (%): 313 (M+, 42), 282 (28), 165 (43), 161 (100), 144 (75), 137 (26), 119 (76), 91 (46), 65 (13).

**4.2.1.3. (4*S*,5*S*)-2-Ethyl-4-hydroxymethyl-5-[4-(methylthio)phenyl]-2-oxazoline 10.** The reaction using propionitrile (3.56 mL, 50 mmol) was carried at 115 °C for 11 h. IR (KBr), $\nu$ ($cm^{-1}$): 3161 (OH), 1669 (C=N); $^1H$ NMR ($CDCl_3$ + $D_2O$) $\delta$: 1.26 (t, $J$ = 7.7 Hz, 3H, $CH_2CH_3$), 2.41 (dq, $J$ = 7.6, 1.2 Hz, 2H, $CH_2CH_3$), 2.48 (s, 3H, $SCH_3$), 3.64 (dd, $J$ = 11.8, 4.1 Hz, 1H, C*H*HOH), 3.90 (dd, $J$ = 11.8, 3.6 Hz, 1H, CH*H*OH), 4.01 (ttd, $J$ = 7.7, 3.8, 1.2 Hz, 1H, H-4), 4.77 (br s, 1H, HOD), 5.26 (d, $J$ = 7.7 Hz, 1H, H-5), 7.19–7.27 (m, 4H, ArH); EIMS *m*/*z* (%): 251 (M+, 48), 165 (17), 137 (19), 117 (11), 99 (100), 82 (44), 57 (18).

**4.2.1.4. (4*S*,5*S*)-4-Hydroxymethyl-2-*iso*-propyl-5-[4-(methylthio)phenyl]-2-oxazoline 11.** The reaction with *iso*-butyronitrile (3.6 mL, 40 mmol) was carried at 105 °C for 7.5 h. IR (KBr), $\nu$ ($cm^{-1}$): 3313 (OH), 1661 (C=N); $^1H$ NMR ($CDCl_3$ + $D_2O$) $\delta$: 1.27 (d, $J$ = 7.1 Hz, 6H, $CH(CH_3)_2$), 2.48 (s, 3H, $SCH_3$), 2.69 (dsp, $J$ = 7.1, 1.0 Hz, 1H, C*H*$(CH_3)_2$), 3.65 (dd, $J$ = 11.5, 4.4 Hz, 1H, C*H*HOH), 3.89 (dd, $J$ = 11.5, 3.8 Hz, 1H, CH*H*OH), 4.01 (dtd, $J$ = 7.5, 4.1, 1.0 Hz, 1H, H-4), 4.76 (br s, 1H, HOD), 5.24 (d, $J$ = 7.7 Hz, 1H, H-5), 7.17–7.28 (m, 4H, ArH); EIMS *m*/*z* (%): 265 ($M^+$, 59), 165 (19), 137 (17), 113 (100), 96 (47), 54 (10), 43 (30), 18 (11).

**4.2.2. (4*S*,5*S*)-4-Hydroxymethyl-2-methyl-5-[4-(methylthio)phenyl]-2-oxazoline 9.[20]** A solution of (2*S*,3*S*)-(+)-thiomicamine **6** (10.66 g, 50 mmol), triethyl orthoacetate (1.2 equiv, 10.8 mL, 60 mmol) and acetic acid (125 μL, 2–4 mol%) in 1,2-dichloroethane (100 mL) was

heated at reflux for 1.5 h. After cooling to ambient temperature, the mixture was poured into 20% $KHCO_3$ and extracted with $CH_2Cl_2$, dried and condensed under reduced pressure to give 11.78 g yellow residue. It was crystallized from $CH_2Cl_2$/hexane to afford 7.47 g (*Y*: 63%) of **9**. IR (KBr), $\nu$ ($cm^{-1}$): 3225 (OH), 1672 (C=N); $^1H$ NMR ($CDCl_3 + D_2O$) $\delta$: 2.10 (d, $J = 1.4$ Hz, 3H, $CCH_3$), 2.48 (s, 3H, $SCH_3$) 3.63 (dd, $J = 11.8$, 4.1 Hz, 1H, $CHHOCH_3$), 3.91 (dd, $J = 11.8$, 3.6 Hz, 1H, $CHHOCH_3$), 4.05–4.11 (m, 1H, H-4), 4.78 (br s, 1H, HOD), 5.24 (d, $J = 7.1$ Hz, 1H, H-5), 7.20–7.28 (m, 4H, ArH); EIMS *m*/*z* (%): 237 (M+, 55), 165 (17), 151 (12), 137 (23), 117 (17), 85 (100), 68 (44).

### 4.3. *O*-Methylation of oxazolines 7–11

#### 4.3.1. Reaction in DMF

**4.3.1.1. (4*S*,5*S*)-4-Methoxymethyl-2-(2-methoxyphenyl)-5-[4-(methylthio)phenyl]-2-oxazoline 14.** To oxazoline **7** (3.15 g, 10 mmol) in DMF (29 mL), NaH (1.2 g, 25 mmol) was added portionwise at ice-bath temperature. The mixture was stirred at this temperature for 1 h before $CH_3I$ (1.6 mL, 26 mmol) was added. The whole mixture was stirred at rt for 18 h, then poured onto ice. After rt was reached the mixture was extracted with ethyl ether until the Dragendorff test was negative. The combined organic extracts were dried and evaporated. The TLC-pure oxazoline **14** (yellow oil, *Y*: 94%) was used as ligand without further purification. IR (film), $\nu$ ($cm^{-1}$): 1648 (C=N); $^1H$ NMR ($CDCl_3$) $\delta$: 2.48 (s, 3H, $SCH_3$), 3.44 (s, 3H, $OCH_3$), 3.59 (dd, $J = 9.6$, 7.1 Hz, 1H, $CHHOCH_3$), 3.79 (dd, $J = 9.6$, 4.1 Hz, 1H, $CHHOCH_3$), 3.93 (s, 3H, $ArOCH_3$), 4.34 (ddd, $J = 7.1$, 6.9, 4.1 Hz, 1H, H-4), 5.44 (d, $J = 6.9$ Hz, 1H, H-5), 6.97–7.03 (m, 2H, ArH), 7.24–7.35 (m, 4H, ArH), 7.42–7.48 (m, 1H, ArH), 7.83–7.86 (m, 1H, ArH), 8.03–8.06 (m, 2H, ArH); EIMS *m*/*z* (%): 343 (M+, 21), 298 (85), 192 (43), 165 (78), 160 (100), 152 (18), 135 (70), 119 (20), 91 (13), 77 (30).

**4.3.2. Reaction in THF. General procedure.** To a suspension of NaH (1.44 g, 30 mmol), in THF (53 mL), $CH_3I$ (2.2 mL, 35 mmol) was added under an argon atmosphere at 0 °C. Then 4-hydroxymethyl-2-oxazoline (20 mmol) was added slowly in THF (50 mL). The mixture was stirred at rt for 17 h, then poured onto ice. At ambient temperature crystalline oxazoline **15** was collected, while in the case of oily products, **16**–**18**, the reaction mixture was extracted with ethyl ether until the Dragendorff test was negative. Then the organic extracts were dried and evaporated to give crude products, pure enough to be used without further purification.

**4.3.2.1. (4*S*,5*S*)-4-Methoxymethyl-5-[4-(methylthio)phenyl]-2-(3-tolyl)-2-oxazoline 15.** IR (KBr), $\nu$ ($cm^{-1}$): 1649 (C=N); $^1H$ NMR ($CDCl_3$) $\delta$: 2.39 (s, 3H, $PhCH_3$), 2.48 (s, 3H, $SCH_3$), 3.43 (s, 3H, $OCH_3$), 3.60 (dd, $J = 9.6$, 6.6 Hz, 1H, $CHHOCH_3$), 3.73 (dd, $J = 9.6$, 4.4 Hz, 1H, $CHHOCH_3$), 4.30 (ddd, $J = 6.9$, 6.6, 4.4 Hz, 1H, H-4), 5.44 (d, $J = 6.9$ Hz, 1H, H-5), 7.24–7.33 (m, 6H, ArH), 7.81–7.88 (m, 2H, ArH); EIMS *m*/*z* (%): 327 (M+, 20), 282 (41), 192 (56), 175 (23), 165 (100), 160 (27), 144 (80), 137 (37), 119 (56), 91 (50), 65 (16).

**4.3.2.2. (4*S*,5*S*)-4-Methoxymethyl-2-methyl-5-[4-(methylthio)phenyl]-2-oxazoline 16.** Yellow oil. IR (film), $\nu$ ($cm^{-1}$): 1675 (C=N); $^1H$ NMR ($CDCl_3$) $\delta$: 2.09 (d, $J = 1.4$ Hz, 3H, $CCH_3$), 2.48 (s, 3H, $SCH_3$), 3.41 (s, 3H, $OCH_3$), 3.51 (dd, $J = 9.6$, 6.3 Hz, 1H, $CHHOCH_3$), 3.60 (dd, $J = 9.6$, 4.4 Hz, 1H, $CHHOCH_3$), 4.08 (qddd, $J = 7.1$, 6.3, 4.4, 1.4 Hz, 1H, H-4), 5.24 (d, $J = 7.1$ Hz, 1H, H-5), 7.20–7.28 (m, 4H, ArH); EIMS *m*/*z* (%): 251 (M+, 54), 206 (100), 192 (37), 165 (44), 137 (33), 117 (27), 99 (53), 84 (21), 68 (67), 57 (56).

**4.3.2.3. (4*S*,5*S*)-2-Ethyl-4-methoxymethyl-5-[4-(methylthio)phenyl]-2-oxazoline 17.** Yellow oil. IR (film), $\nu$ ($cm^{-1}$): 1668 (C=N); $^1H$ NMR ($CDCl_3$) $\delta$: 1.26 (t, $J = 7.5$ Hz, 3H, $CH_2CH_3$), 2.41 (dq, $J = 7.5$, 1.3 Hz, 2H, $CH_2CH_3$), 2.48 (s, 3H, $SCH_3$), 3.41 (s, 3H, $OCH_3$), 3.49 (dd, $J = 9.6$, 6.6 Hz, 1H, $CHHOCH_3$), 3.62 (dd, $J = 9.6$, 4.4 Hz, 1H, $CHHOCH_3$), 4.08 (tdt, $J = 6.7$, 4.4, 1.3 Hz, 1H, H-4), 5.24 (d, $J = 6.9$ Hz, 1H, H-5), 7.17–7.37 (m, 4H, ArH); EIMS *m*/*z* (%): 265 (M+, 63), 220 (87), 192 (43), 165 (53), 137 (32), 117 (18), 113 (66), 98 (47), 82 (100), 57 (46), 45 (34), 29 (36), 18 (58).

**4.3.2.4. (4*S*,5*S*)-2-*iso*-Propyl-4-methoxymethyl-5-[4-(methylthio)phenyl]-2-oxazoline 18.** Yellow oil. IR (film), $\nu$ ($cm^{-1}$): 1665 (C=N); $^1H$ NMR ($CDCl_3$) $\delta$: 1.27 (d, $J = 6.9$ Hz, 6H, $CH(CH_3)_2$), 2.48 (s, 3H, $SCH_3$), 2.69 (dsp, $J = 6.9$, 1.0 Hz, 1H, $CH(CH_3)_2$), 3.40 (s, 3H, $OCH_3$), 3.46 (dd, $J = 9.6$, 6.7 Hz, 1H, $CHHOCH_3$), 3.64 (dd, $J = 9.6$, 4.4 Hz, 1H, $CHHOCH_3$), 4.07 (ddt, $J = 6.6$, 4.4, 1.0 Hz, 1H, H-4), 5.24 (d, $J = 6.6$ Hz, 1H, H-5), 7.19–7.30 (m, 4H, ArH); EIMS *m*/*z* (%): 279 (M+, 37), 234 (68), 192 (40), 165 (63), 151 (11), 137 (32), 127 (61), 117 (10), 112 (29), 96 (100), 54 (24).

### 4.4. Sulfonation of oxazolines 25 and 9

**4.4.1. (4*S*,5*S*)-4-Mesyloxymethyl-5-[4-(methylthio)phenyl]-2-phenyl-2-oxazoline 12.** To a suspension of oxazoline **25**[21] (2.99 g, 10 mmol) in THF (40 mL) mesyl chloride (1.6 mL, 20 mmol) and $Et_3N$ (2.7 mL, 20 mmol) were added at 0 °C. The mixture was kept at this temperature for 18 h, then at rt it was washed with satd $NaHCO_3$. The aqueous phase was extracted with AcOEt until the Dragendorff test was negative. The combined organic extracts were washed with brine, dried, and evaporated to give crude oxazoline **12**. IR (KBr), $\nu$ ($cm^{-1}$): 1644 (C=N); $^1H$ NMR ($CDCl_3$) $\delta$: 2.48 (s, 3H, $SCH_3$), 3.05 (s, 3H, $SO_2CH_3$), 4.40–4.46 (m, 2H, $CH_2OMs$), 4.49–4.51 (m, 1H, H-4), 5.50 (d, $J = 6.9$ Hz, 1H, H-5), 7.25–7.28 (m, 4H, ArH), 7.43–7.58 (m, 3H, ArH), 8.00–8.04 (m, 2H, ArH); EIMS *m*/*z* (%): 377 (M+, 14), 225 (35), 146 (53), 137 (10), 130 (100), 105 (63), 77 (38).

**4.4.2. (4*S*,5*S*)-2-Methyl-5-[4-(methylthio)phenyl]-4-tosyloxymethyl-2-oxazoline 19.** To a solution of oxazoline **9** (0.237 g, 1 mmol) and triethylamine (0.33 mL, 2.5 mmol) in $CH_2Cl_2$ (2 mL) *p*-toluenesulfonyl chloride (0.24 g, 1.25 mmol) was added portionwise at 0 °C. The mixture was kept at this temperature for 48 h. After rt was

reached, the crystals of $Et_3N{\cdot}HCl$ were removed by filtration and filtrate was washed with 1% NaOH ($2\times10$ mL), 20% $NH_4Cl$ and water (25 mL), dried ($Na_2SO_4$) and concentrated. The crude product was crystallized from methanol to give pure oxazoline **19** as a colorless crystals. IR (KBr), $\nu$ ($cm^{-1}$): 1669 (C=N); $^1H$ NMR ($CDCl_3$) $\delta$: 2.05 (d, $J = 1.1$ Hz, 3H, $CCH_3$), 2.46 (s, 3H, $ArCH_3$), 2.49 (s, 3H, $SCH_3$), 4.05–4.11 (m, 2H, $CH_2OTs$), 4.28–4.38 (m, 1H, H-4), 5.24 (d, $J = 6.0$ Hz, 1H, H-5), 7.13–7.36 (m, 6H, ArH), 7.70–7.81 (m, 2H, ArH); EIMS *m*/*z* (%): 391 (M+, 37), 219 (23), 206 (81), 175 (35), 137 (24), 133 (93), 91 (72), 84 (60), 68 (100), 44 (43).

### 4.5. *O*-Silylation of oxazolines 9 and 25. General procedure

The oxazoline (1 mmol), TBDMSCl (0.30 g, 2 mmol), and imidazole (0.15 g, 2.2 mmol) in DMF (1 mL) were stirred at rt for 1.5 h, then poured onto ice (7 g). When the mixture reached rt it was extracted with ethyl ether until the Dragendorff test was negative. The organic extracts were dried and the solvent evaporated. TLC-pure oxazolines **20** and **21** were used as ligand without further purification.

**4.5.1. (4*S*,5*S*)-4-[(*t*-Butyl)dimethylsilyloxy]methyl-2-methyl-5-[4-(methylthio)phenyl]-2-oxazoline 20.** Colorless oil. IR (film), $\nu$ ($cm^{-1}$): 1646 (C=N), 1252, 814 (Si-$CH_3$); $^1H$ NMR ($CDCl_3$) $\delta$: 0.07 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 2.08 (d, $J = 1.1$ Hz, 3H, $CH_3$), 2.48 (s, 3H, $SCH_3$), 3.63 (dd, $J = 10.2$, 6.9 Hz, 1H, C*H*HOSi), 3.87 (dd, $J = 10.2$, 3.8 Hz, 1H, CH*H*OSi), 3.99 (qddd, $J = 6.9$, 6.3, 3.8, 1.4 Hz, 1H, H-4), 5.32 (d, $J = 6.3$ Hz, 1H, H-5), 7.20–7.27 (m, 4H, ArH); EIMS *m*/*z* (%): 351 (M+, 1), 294 (50), 264 (49), 252 (19), 206 (18), 190 (10), 142 (10), 137 (100), 73 (26).

**4.5.2. (4*S*,5*S*)-4-[(*t*-Butyl)dimethylsilyloxy]methyl-5-[4-(methylthio)phenyl]-2-phenyl-2-oxazoline 21.** Colorless oil. IR (film), $\nu$ ($cm^{-1}$): 1650 (C=N), 1253, 814 (Si-$CH_3$); $^1H$ NMR ($CDCl_3$) $\delta$: 0.07 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 2.48 (s, 3H, $SCH_3$), 3.74 (dd, $J = 10.2$, 7.1 Hz, 1H, C*H*HOSi), 4.01 (dd, $J = 10.2$, 3.8 Hz, 1H, CH*H*OSi), 4.22 (ddd, $J = 7.1$, 6.0, 3.8 Hz, 1H, H-4), 5.53 (d, $J = 6.0$ Hz, 1H, H-5), 7.23–7.53 (m, 7H, ArH), 8.00–8.03 (m, 2H, ArH); EIMS *m*/*z* (%): 413 (M+, 1), 356 (100), 326 (52), 268 (22), 165 (17), 137 (80), 105 (58), 77 (22), 73 (18).

### 4.6. (4*S*,5*S*)-5-[4-(Methylthio)phenyl]-2-phenyl-4-phenoxymethyl-2-oxazoline 22

Oxazoline **26**[12] (453 mg, 1 mmol) was stirred with phenol (0.113 g, 1.2 mmol) and $K_2CO_3$ (0.70 g, 5 mmol) in DMF (10 mL) at rt for 48 h, then poured onto ice. After rt was reached the solid was filtered off. It was washed with water and air-dried to give crude product. Crystallization from EtOH/*i*-$Pr_2O$ afforded pure oxazoline **22** as a colorless crystals. IR (KBr), $\nu$ ($cm^{-1}$): 1645 (C=N); $^1H$ NMR ($CDCl_3$) $\delta$: 2.49 (s, 3H, $ArSCH_3$), 4.11 (dd, $J = 9.3$, 7.7 Hz, 1H, C*H*HOPh), 4.38 (dd, $J = 9.3$, 4.1 Hz, 1H, CH*H*OPh), 4.55 (ddd, $J = 7.7$, 6.6, 4.1 Hz, 1H, H-4), 5.60 (d, $J = 6.6$ Hz, 1H, H-5), 6.93–7.00 (m, 3H, ArH), 7.26–7.35 (m, 6H, ArH), 7.43–7.57 (m, 3H, ArH), 8.04–8.07 (m, 2H, ArH); EIMS *m*/*z* (%): 375 (M+, 60), 345 (100), 281 (14), 268 (74), 240 (12), 223 (12), 165 (98), 151 (11), 137 (26), 133 (93), 105 (44), 91 (72), 84 (60), 68 (100), 44 (43).

### 4.7. (4*S*,5*S*)-5-[4-(Methylthio)phenyl]-2-phenyl-4-tolylthiomethyl-2-oxazoline 24

To a mixture of *p*-methyl-thiophenol (1.24 g, 10 mmol) in DMF (8 mL), NaH (0.480 g, 10 mmol) was added at 0 °C. After half an hour mesylate **12** (1.51 g, 4 mmol) in DMF (10 mL) was added. The mixture was stirred at this temperature for 20 h, then poured onto ice. After rt was reached the solid was filtered off, dissolved in ethyl ether, washed with 5% NaOH ($2\times10$ mL) and 20% $NH_4Cl$ ($2\times10$ mL) and dried. The crude product was crystallized from $Et_2O$ to give oxazoline **24** as colorless crystals. IR (KBr), $\nu$ ($cm^{-1}$): 1640 (C=N); $^1H$ NMR ($CDCl_3$) $\delta$: 2.29 (s, 3H, $ArCH_3$), 2.48 (s, 3H, $SCH_3$), 2.98 (dd, $J = 13.5$, 9.3 Hz, 1H, C*H*HSAr), 3.49 (dd, $J = 13.5$, 3.8 Hz, 1H, CH*H*SAr), 4.30 (ddd, $J = 9.3$, 6.0, 3.8 Hz, 1H, H-4), 5.50 (d, $J = 6.0$ Hz, 1H, H-5), 7.03–7.06 (m, 2H, ArH), 7.21–7.28 (m, 6H, ArH), 7.41–7.55 (m, 3H, ArH), 7.98–8.00 (m, 2H, ArH); EIMS *m*/*z* (%): 405 (M+, 12), 358 (59), 268 (59), 165 (100), 137 (52), 130 (86), 123 (12), 105 (69), 91 (16), 77 (56).

### 4.8. Synthesis of oxazoline 23

**4.8.1. (4*S*,5*S*)-5-[4-(Methylthio)phenyl]-2-phenyl-4-thioacetoxylmethyl-2-oxazoline 13.** Mesylate **12** (2.17 g, 5.76 mmol) and potassium thioacetate (6.05 g, 53 mmol) in DMF (50 mL) were stirred at rt for 21 h, then poured onto ice. After rt was reached the solid was filtered off, air-dried and crystallized from $CHCl_3$ to give colorless crystals. IR (KBr), $\nu$ ($cm^{-1}$): 1642 (C=N), 1688 ($SCOCH_3$); $^1H$ NMR ($CDCl_3$) $\delta$: 2.38 (s, 3H, $SCOCH_3$), 2.48 (s, 3H, $SCH_3$), 3.31 (dd, $J = 13.7$, 6.0 Hz, 1H, C*H*HSCOCH$_3$), 3.43 (dd, $J = 13.7$, 4.9 Hz, 1H, CH*H*SCOCH$_3$), 4.40 (ddd, $J = 6.9$, 6.0, 4.9 Hz, 1H, H-4), 5.22 (d, $J = 6.9$ Hz, 1H, H-5), 7.23–7.29 (m, 3H, ArH), 7.41–7.55 (m, 4H, ArH), 8.00–8.04 (m, 2H, ArH); EIMS *m*/*z* (%): 357 (M+, 8), 282 (43), 268 (34), 165 (27), 162 (100), 137 (18), 130 (73), 105 (41), 77 (42), 59 (16).

**4.8.2. (4*S*,5*S*)-5-[4-(Methylthio)phenyl]-2-phenyl-4-thiomethoxymethyl-2-oxazoline 23.** The oxazoline **13** (1.071 g, 3 mmol) was stirred in 5% methanolic KOH solution (2.1 equiv KOH, 7.5 mL) at rt for 24 h under an argon atmosphere. The mixture was concentrated under reduced pressure, the residue was dissolved in DMF (9 mL), cooled to 0 °C and treated with $CH_3I$ (0.77 mL, 12 mmol). The mixture was stirred at rt for 24 h, then poured onto ice. At ambient temperature it was extracted with $CH_2Cl_2$ until the Dragendorff test was negative and washed with 20% $NH_4Cl$. The organic extracts were dried and the solvent evaporated. The residue was crystallized from $CH_2Cl_2$/hexane to afford colorless crystals. IR (KBr), $\nu$ ($cm^{-1}$): 1644 (C=N); $^1H$ NMR

($CDCl_3$) $\delta$: 2.13 (s, 3H, $CH_2SCH_3$), 2.48 (s, 3H, $ArSCH_3$), 2.71 (dd, $J = 13.5$, 8.5 Hz, 1H, $CHHSCH_3$), 3.03 (dd, $J = 13.5$, 4.1 Hz, 1H, $CHHSCH_3$), 4.33–4.39 (m, 1H, H-4), 5.47 (d, $J = 6.0$ Hz, 1H, H-5), 7.24–7.33 (m, 4H, ArH), 7.42–7.56 (m, 3H, ArH), 8.02–8.06 (m, 2H, ArH); EIMS *m/z* (%): 329 (M+, 11), 268 (97), 208 (48), 165 (75), 162 (22), 150 (16), 137 (47), 130 (100), 122 (17), 105 (89), 91 (12), 77 (80), 61 (26), 51 (16).

### 4.9. Addition of $CH_3Li$ to imine 1. General procedure

A mixture of imine **1** (0.127 g, 0.5 mmol) and the ligand **16** (0.326 g, 1.3 mmol) in toluene (30 mL) was stirred under argon atmosphere at −65 °C for 1 h. $CH_3Li$ (1.6 M solution in ether, 0.78 mL, 1.25 mmol) was added and stirring was continued until no more amine **3** was produced (ca. 2.5 h, TLC). The reaction mixture was quenched with 20% $NH_4Cl$ at −65 °C and, at ambient temperature, phases were separated and the aqueous one was extracted with ethyl ether until the Dragendorff test was negative. The yields and ee of the product resulting from many experiments are shown in Table 2. The enantiomeric excess of amine **3** was established by HPLC of the crude products mixture (Chiracel OD-H column, 2% v/v 2-propanol in hexane, flow 0.5 mL/min, 229 nm; retention times: 26 min-enantiomer (*R*), 28.5 min-enantiomer (*S*)). The crude product was purified by column chromatography on silica gel (1:20) with $CH_2Cl_2/Et_3N$: 100/1. Spectral characteristics of the oily base **3**, corresponded to the literature data.[12] The (*S*)-configuration of major enantiomer of amine **3** was established by HPLC comparison with a sample of (*S*)-(−)-3, after transformation into (*S*)-salsolidine **4** of known absolute stereochemistry.[15]

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