Pergamon

Tetrahedron 55 (1999) 5377–5388

TETRAHEDRON

Synthesis of Chiral Tridentate Oxazolines with Thioether and Heteroaryl Donor Groups and their Application in the Catalysis of Asymmetric Michael Reactions

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Received 22 January 1999; revised 26 February 1999; accepted 10 March 1999

Abstract

Four chiral amino alcohols **1** derived from the natural α-amino acids *L*-cysteine and *L*-methionine have been converted with 2-thiophene and 2-pyridine carboxylic acid derivatives **2** to give eight tridentate oxazoline ligands **3a-d** and **4a-d** with a heteroaryl and a thioether donor function. In one case the coordination geometry at copper(II) was established by X-ray single crystal structure analysis. All ligands have been screened with 13 metal compounds **8** with regard to the asymmetric catalysis of the Michael reaction of a β-keto ester **6** with methyl vinyl ketone (**7**) to give an optimal result of 19% *ee*. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Asymmetric reactions; Catalysis; Michael reactions; Oxazolines

1. Introduction

C_2-symmetric bis(oxazolines) [1] have become one of the leading classes of chiral ligands [2] in catalytic asymmetric synthesis [3], and a number of outstanding applications in the catalysis of C–C bond formations has been reported [4–6]. But also many bidentate ligands bearing only one oxazoline moiety and another different donor function are precedented [7–9], and in some cases the latter was reported to be a heteroaryl group [10,11]. With respect to this, 2-pyridyloxazolines have found particular broad applications [12–20], whereas thiophene as the second donor function is rarely reported [21,22].

In the course of our efforts toward the asymmetric catalysis of the Michael reaction [23] we are particularly interested in the synthesis of tridentate ligands [24,25]. In this context we wish

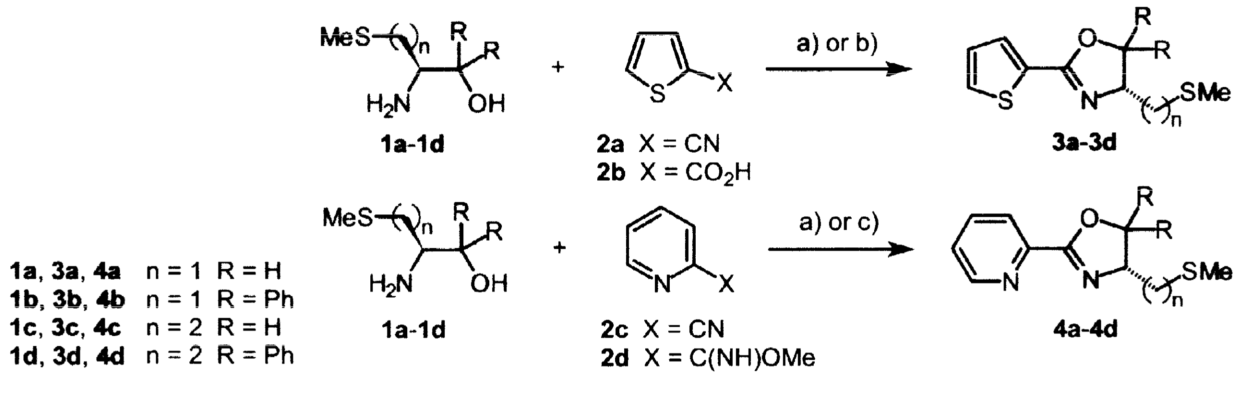
PII: S0040-4020(99)00235-5

to report on a number of chiral tridentate oxazoline ligands **3** and **4**[1] with additional heteroaryl (pyridine and thiophene) and thioether donor groups. The eight compounds **3a**–**3d** and **4a**–**4d** (Scheme 1) have a modular constitution and have been accessed from thiophene and pyridine carboxylic acid derivatives **2a**–**d** and four different amino alcohols **1a**–**d** derived from the natural amino acids *L*-cysteine and *L*-methionine.

2. Results and discussion

2.1 Ligand Synthesis

The natural sulfur containing amino acids *L*-cysteine and *L*-methionine are highly functionalized chiral building blocks, which are converted to the amino alcohols **1a** [31], **1b** [32], **1c**, and **1d** [32] by standard procedures. There is a number of established synthetic methods for the preparation of oxazolines from amino alcohols and carboxylic acid derivatives [33], but also new procedures and protocols are present in the recent literature [34–36]. The synthesis of the compounds **3a**–**3d** and **4a**–**4d** is summarized in Scheme 1. The oxazolines **3a**, **3c** and **4a** were prepared by the zinc-catalyzed condensation of carbonitriles with amino alcohols according to the method of Witte and Seeliger (a) [37]. For the synthesis of the ligands **3b** and **3d** the carboxylic acid was activated with PPh_3–CCl_4 (*in situ*–formation of the acid chloride) and then directly converted with the amino alcohol following the protocol of Vorbrüggen and Krolikiewicz [38]. Another convenient route to oxazolines is based on the acid–catalyzed condensation of the imido ester **2d** [39] with amino alcoholes which led to the formation of the ligands **4b**, **4c** and **4d** (c) [40]. Yields for **3a**–**3d** and **4a**–**4d** are summarized in Table 1. All compounds were obtained in good to satisfying yields, and complete characterization data are given in the experimental section.[2]



Scheme 1. Formation of oxazolines from 1.0 eq. amino alcohol **1** and 1.0 eq. carboxylic acid derivative **2**; reagents and conditions: a) 0.03–0.05 eq. $ZnCl_2$, PhCl, 16 h, 135°C; b) 3 eq. PPh_3, 4 eq. CCl_4, 4 eq. NEt_3, pyridine–MeCN (1 : 1), 24 h, room temp.; c) cat. HCl–H_2O, PhCl, 24 h, 80°C.

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[1] For other tridentate and tetradentate oxazolines see ref [26-30].

[2] Except for compound **4c**, which was reported before by *Brunner et al.* [40,41].

Table 1. Products, yields, starting materials, and conditions.

Product	Yield	Starting materials		Method
3a	67%	**1a**	**2a**	a
3b	44%	**1b**	**2b**	b
3c	62%	**1c**	**2a**	a
3d	62%	**1d**	**2b**	b
4a	36%	**1a**	**2c**	a
4b	65%	**1b**	**2d**	c
4c	55%	**1c**	**2d**	c
4d	53%	**1d**	**2d**	c

2.2 Structural Investigation

We are interested in the coordination geometry of these new ligands in complexes with transition metals; in particular, we were wondering whether the tridentate ligands would occupy three facial or three meridianal positions in an octahedron or even be bridging between metal centers in a polynuclear complex.

To date, we were only able to obtain crystals suitable for structure elucidation of ligand **3a** coordinated to copper(II). In detail, single crystals of complex **5** were obtained by slow diffusion of hexane into an ethanolic solution of **3a** and $Cu(BF_4)_2$. The molecular structure of **5** was determined by X-ray structure analysis to be the 2 : 1 adduct of **3a** with $Cu(II)(BF_4)_2$; an ORTEP plot is provided in Figure 1.[3]

The center metal is coordinated by only four of the six donor atoms (namely, the oxazoline-N and the thioether-S atoms) in a planar fashion [bond angles: S(2)–Cu–S(4) 92.4°, S(2)–Cu–N(1) 85.1°, S(4)–Cu–N(2) 84.7°, N(1)–Cu–N(2) 98.5°, sum: 360.7°]. There are two arrangements of the oxazoline ligands that allow for a square planar geometry: At first glance a coordination appears to be less sterically demanding where the thiophene moieties are located at different sides of the square. But complex **5** is found to be in the *cis*-configuration, where the thiophene rings are close to each other. This situation may be preferred, because the π-accepting *S*-centers are trans to the σ-donating *N*-centers. The thiophene moieties theirselves of both ligands do not have any close contact to Cu. Instead, both BF_4 counterions seem to be located at the fifth and sixth coordination site to fill up a highly Jahn-Teller distorted octahedron. However, exact Cu–F distances could not be extracted due to the highly disordered BF_4 groups. Both five membered-rings in each ligand are about coplanar and connected by a C–C bond, which is significantly shortened compared to a C–C single bond. Interestingly, they are holding a conformation, in which thiophene-S and oxazoline-N are antiperiplanar.

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[3] Further details of the crystal structure investigation may be obtained from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ (UK), on quoting the full journal citation and the deposition number 102784.

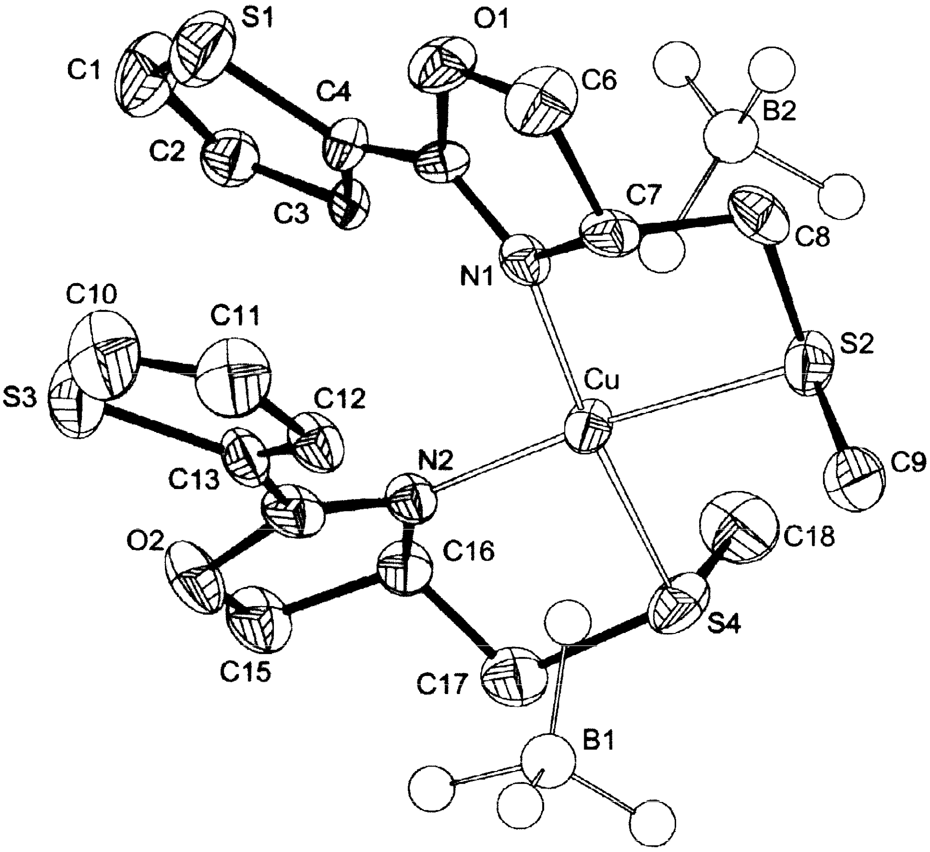
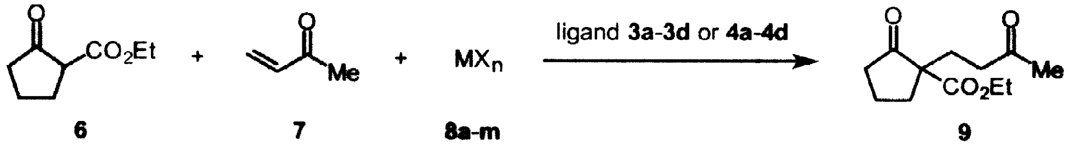


Figure 1. Crystal structure of **5**. Selected bond distances in Å: Cu–S(2) 2.380(2), Cu–S(4) 2.370(2), Cu–N(1) 1.985(4), Cu–N(2) 1.942(4), N(1)–C(5) 1.277(7), C(4)–C(5) 1.453(8).

2.3 Michael Reaction

As already mentioned in the introduction, we are interested in the transition metal catalysis of asymmetric Michael reactions. Recently, Shibasaki et al. [42,43] have introduced an excellent heterobimetallic catalyst for the Michael reaction of β-dicarbonyl compounds with α,β-unsaturated ketones. However, these systems are basic and require inert and anhydrous conditions. Those basic reaction conditions often cause a number of unwanted side- and subsequent processes, namely ester-solvolyses, aldol-cyclizations and retro-Claisen decompositions, which are avoided by neutral transition metal catalysts. In the past years only a small number of chiral catalysts has been reported, which are avoiding strongly basic conditions [26,44–46]

In this context we have screened the catalytic activity of our eight ligands **3a**–**3d** and **4a**–**4d** separately together with 13 metal salts **8a**–**8m** (from which we knew that they are at least to some extent catalyzing the Michael reaction) concerning the asymmetric catalysis of the reaction of β-keto ester **6** with methyl vinyl ketone (**7**) forming product **9**.



8a-m

8a	$CrCl_3 \cdot 6\,H_2O$
8b	$Mn(OAc)_2 \cdot 4\,H_2O$
8c	$FeCl_3 \cdot 6\,H_2O$
8d	$Ni(OAc)_2 \cdot 4\,H_2O$
8e	$NiCl_2 \cdot 6\,H_2O$
8f	$Co(OAc)_2 \cdot 4\,H_2O$
8g	$CoCl_2 \cdot 6\,H_2O$
8h	$RhCl_3 \cdot 3\,H_2O$
8i	$Cu(OAc)_2 \cdot H_2O$
8j	AgOAc
8k	$ZnCl_2$
8l	$SnCl_2$
8m	$Pb(OAc)_2 \cdot 3\,H_2O$

Scheme 2. Metal catalyzed Michael reaction, screening of ligands 3a–3d and **4a–4d** with metal compounds **8a–m**.

Practically, 1.0 eq. of donor **6** was treated with 0.05 eq. of the metal compound **8a–8m** and 0.075 eq. of the oxazoline **3a–3d** or **4a–4d** in CH_2Cl_2 as solvent at room temperature. After equilibration (1 to 2 h) a small excess of the acceptor **7** (1.1 to 1.5 eq.) was added and after stirring the mixture overnight at room temperature all metal containing materials were removed by filtration over SiO_2. Importantly, all conversions were performed without exclusion of moisture and air. Analysis of the reaction mixtures and of the enantiometric excess of **9**[4,5] was performed by chiral GC. Conversions were usually greater than 10% with all compounds **8a–8m**, with Fe(III) and Ni(II) (and some other single metal-ligand combinations) even greater than 95%. Moreover, it was checked that chiral oxazolines theirselves without any metal compound did not catalyze the conversion of **6** and **7** significantly.

In respect of enantioselectivity, *ee*'s different from zero were obtained only with the pyridine ligands **4a–4d**; thiophenes **3a–3d** did not show selectivities at all. Moreover, the *ee* exceeded 10% only with ligand **4d** in combination with Ni- and Co-acetates (**8d**, **8f**, results are compiled in Table 2). These results were taken as the base for further optimization of the parameters ligand-to-metal ratio and temperature. It turned out that the initially chosen conditions were the optimal ones (room temp. and ligand / metal = 1.5). Both results, temperature and ligand-to-metal ratio dependence obviously indicate that equilibria and more than one catalytically active species are present in the reaction mixture.

In summary, this combinatorial-type of approach by testing a large number of ligand-metal combinations *in situ* showed that the ligand **4d** might be suited in combination with Ni(II) to give a new asymmetric catalyst for the Michael reaction of β-keto esters with enones. How-

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[4] The asymmetric synthesis of **9** was reported twice before [47,48].

[5] Full spectral data of **9** can be found at the following place: [49].

ever, further experiments – including isolation and investigation of unique Ni(II) complexes – are necessary and already subject of current work in our laboratory.

Table 2. Screening results of ligand **4d** with metal salts **8d** and **8f**.

Metal salt	Ligand	Ligand / Metal	Temp. / °C	ee / %
8d	**4d**	1.5	25	19
8d	**4d**	1.5	40	17
8d	**4d**	1.5	10	8
8d	**4d**	1.5	0	6
8d	**4d**	1.0	25	13
8d	**4d**	3.0	25	10
8f	**4d**	1.5	25	10
8f	**4d**	1.5	0	8

2.4 *Summary*

Eight different tridentate oxazoline ligands with adjacent thioether and heteroaryl donor groups were prepared. Starting materials were chiral amino alcoholes derived from the naturally α-amino acids *L*-cysteine and *L*-methionine as well as pyridine and thiophene carboxylic acid derivatives. In one example the coordination geometry of two oxazolines to a copper(II) center was determined by X-ray single crystal structure analysis to be square planar. In this case the ligand was bidentate with oxazoline-N and thioether-S atom coordinating to the center metal. The thiophene moieties did not show contact to Cu. Regarding the asymmetric catalysis of the Michael reaction, only pyridine ligand **4d** derived from methionine in combination with $Ni(OAc)_2 \cdot 4\ H_2O$ seems to be promising for further optimizations.

3. Experimental[6]

3.1 *General*

Column chromatography was accomplished with Merck silica gel (Type 60, 0.063–0.200 mm). ^1H NMR spectra were recorded on a Bruker AM 400 (400 MHz) at 25°C using the residual proton solvent peak of $CDCl_3$ at 7.26 ppm as an internal standard. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50 MHz) at 25°C using the solvent triplet of $CDCl_3$ at 77.0 ppm as an internal standard. Assignments were made using DEPT experiments. MS spectra were obtained with Varian MAT 711 (EI, 70 eV) and MAT 955Q (high resolution, EI, 70 eV and FAB with a NBA matrix). IR spectra were recorded on a Nicolet Magna IR 750 (ATR) and

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[6] Abbreviations: ATR: attenuated total reflection; MTB: *tert.*-butyl methyl ether; PE: petroleum ether (hexanes); th: thienyl; py: pyridyl.

Perkin-Elmer 881 (for KBr pellets), only characteristic bands are listed. Elemental analyses were obtained with an Analytik Jena Vario EL. Optical rotations were measured with a Perkin Elmer polarimeter 341 (1 dm cuvettes, *c* in g/l). Melting points were measured with a Leica Galen III and are uncorrected. Chiral GC-analysis: HP 5890 II with FI detection, a Shimadzu C-R6A integrator, Macherey-Nagel column FS-LIPODEX E (25 m, 0.25 mm), nitrogen carrier gas.

Reagents and starting materials, including compound **1c**, were purchased from common commercial suppliers and used without further purification. Amino alcohols **1a** [31], **1b** [32], and **1d** [32] and imidoester **2d** [39] were prepared according to literature protocols. Solvents were purified and dried following standard procedures.

*3.2 Syntheses of Compounds **3a–d** and **4a–d***

*(R)-(+)-4,5-Dihydro-4-(methylsulfanylmethyl)-2-(2-thienyl)oxazole (**3a**).* A mixture of amino alcohol **1a** (200 mg, 1.65 mmol), thiophene-2-carbonitrile (**2a**) (180 mg, 1.65 mmol) and $ZnCl_2$ (6.7 mg, 0.050 mmol) in dry chlorobenzene (2.5 ml) was stirred under an atmosphere of argon for 16 h at 135°C. After removal of the solvent *in vacuo*, the residue was chromatographed on silica gel (PE / MTB 3 : 1, $R_f = 0.10$) to give 235 mg (1.11 mmol, 67%) of **3a** as a colorless oil. $[\alpha]_D^{20}$ +21 (*c* 5.5, $CHCl_3$). IR: $1/\lambda$ = 3078 (w), 2915 (m), 1643 (vs), 1521 (m), 1432 (s), 1371 (m), 1361 (m), 1254 (m), 1217 (m), 1059 (s), 1018 (s), 951 (m), 852 (m), 714 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3 H; CH_3), 2.59–2.66 (m, 1 H; SCH*H*), 2.91–2.96 (m, 1 H; SC*H*H), 4.26–4.35 (m, 1 H; H–5), 4.48–4.58 (m, 2 H; H–5, H–4), 7.09 (dd, *J* = 4.8, 3.8 Hz, 1 H; th–H–4), 7.48 (dd, *J* = 5.0, 0.8 Hz, 1 H; th–H–5), 7.63 (dd, *J* = 3.8, 0.8 Hz, 1 H; th–H–3) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 19.90 (CH_3), 38.87 (SCH_2), 66.30 (C–4), 72.18 (C–5), 127.40 (th–CH), 129.84 (th–CH), 129.90 (th–C–2), 130.28 (th–CH), 160.03 (C–2) ppm. MS (EI), m/z (%): 213 (M^+, 8), 152 (100), 124 (33), 111 (16), 97 (29). $C_9H_{11}NOS_2$ (213.31): Calcd. C, 50.67; H, 5.20; N, 6.57. Found: C, 50.65; H, 5.31; N, 6.55. Mol. mass calcd. 213.0282; found 213.0281 (M^+, HRMS).

*(R)-(–)-4,5-Dihydro-5,5-diphenyl-4-(methylsulfanylmethyl)-2-(2-thienyl)oxazole (**3b**).* Under an atmosphere of argon a solution of thiophene-2-carboxylic acid (**2b**) (141 mg, 1.10 mmol) and PPh_3 (863 mg, 3.29 mmol) in anhydrous pyridine/MeCN (1 : 1) (1.0 ml) was added gradually to a stirred suspension of amino alcohol **1b** (300 mg, 1.10 mmol), NEt_3 (0.60 ml, 4.4 mmol) and CCl_4 (0.40 ml, 4.4 mmol) in anhydrous pyridine/MeCN (1 : 1) (0.8 ml) within 20 min. After stirring for 24 h at room temp. the mixture was diluted with PE. After filtration, all volatile materials were removed from the filtrate *in vacuo*, and the residue was chromatographed on silica gel (PE / MTB 7 : 1, $R_f = 0.14$) to give 175 mg (0.480 mmol, 44%) of **3b** as a yellow resin, which could not be crystallized. $[\alpha]_D^{20}$ –320 (*c* 6.3, $CHCl_3$). IR: $1/\lambda$ = 2915 (m), 1652 (vs), 1493 (m), 1447 (m), 1431 (s), 1369 (m), 1326 (m), 1061 (m), 967 (m), 756 (s), 699 (vs) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.14 (s, 3 H; CH_3), 2.40–2.42 (m, 2 H; SCH_2), 5.06–

5.09 (m, 1 H; H–4), 7.13 (dd, J = 5.1, 3.7 Hz, 1 H; th–H–4), 7.23–7.37 (m, 6 H; arom. H), 7.39–7.45 (m, 2 H; arom. H), 7.51 (dd, J = 4.9, 1.0 Hz, 1 H; th–H–5), 7.60–7.64 (m, 2 H; arom. H), 7.80 (dd, J = 3.6, 1.0 Hz, 1 H; th–H–3) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 16.82 (CH_3), 37.87 (C–4), 75.57 (SCH_2), 93.18 (C–5), 126.40, 126.65, 127.53, 127.59, 127.83, 127.94, 128.28 (each arom. CH), 129.99 (th–C–2), 130.18, 130.63 (each arom. CH), 139.57, 143.40 (each arom. C), 158.16 (C–2) ppm. MS (EI), m/z (%): 365 (M^+, 2), 304 (54), 238 (42), 195 (61), 183 (15), 168 (62), 136 (83), 111 (83), 84 (100), 69 (87). $C_{21}H_{19}NOS_2$ (365.51): Calcd. C, 69.01; H, 5.24; N, 3.83. Found: C, 69.28; H, 5.58; N, 3.74. Mol. mass calcd. 365.0908; found 365.0912 (M^+, HRMS).

(S)-(–)-4,5-Dihydro-4-(methylsulfanylethyl)-2-(2-thienyl)oxazole (3c). According to the procedure described for compound **3a** the conversion of amino alcohol **1c** (80 mg, 0.59 mmol), thiophene-2-carbonitrile (**2a**) (65 mg, 0.59 mmol) and $ZnCl_2$ (2.4 mg, 0.018 mmol) in chlorobenzene (1.5 ml) afforded after purification by chromatography on silica gel (PE / MTB 3 : 1, R_f = 0.19) 84 mg (0.37 mmol, 62%) of **3c** as a colorless oil. $[\alpha]_D^{20}$ –94 (*c* 6.6, $CHCl_3$). IR: 1/λ = 2914 (m), 1647 (vs), 1433 (s), 1371 (m), 1362 (m), 1055 (s), 1018 (s), 951 (m), 850 (m), 714 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.82–1.91 (m, 1 H; CH*H*), 1.97–2.06 (m, 1 H; C*H*H), 2.13 (s, 3 H; CH_3), 2.59–2.71 (m, 2 H; SCH_2), 4.06 (t, J = 7.8 Hz, 1 H; H–5), 4.36–4.44 (m, 1 H; H–4), 5.52 (dd, J = 9.5, 8.1 Hz, 1 H; H–5), 7.08 (dd, J = 5.1, 3.7 Hz, 1 H; th–H–4), 7.45 (dd, J = 5.1, 1.0 Hz, 1 H; th–H–5), 7.59 (dd, J = 3.6, 0.9 Hz, 1 H; th–H–3) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 15.47 (CH_3), 30.59 (CH_2), 35.22 (SCH_2), 65.89 (C–4), 72.66 (C–5), 127.49 (th–CH), 129.73 (th–CH), 130.24 (th–C–2, th–CH), 159.39 (C–2) ppm. MS (EI), m/z (%): 227 (M^+, 4), 153 (13), 111 (100), 100 (15), 97 (21), 85 (18). $C_{10}H_{13}NOS_2$ (227.34): Calcd. C, 52.83; H, 5.76; N, 6.16. Found: C, 52.78; H, 5.97; N, 6.16. Mol. mass calcd. 227.0439; found 227.0438 (M^+, HRMS).

(S)-(–)-4,5-Dihydro-5,5-diphenyl-4-(methylsulfanylethyl)-2-(2-thienyl)oxazole (3d). According to the procedure described for compound **3b** the conversion of amino alcohol **1d** (200 mg, 0.700 mmol), NEt_3 (0.39 ml, 2.8 mmol) and CCl_4 (0.27 ml, 2.8 mmol) in pyridine/MeCN (0.8 ml) with thiophene-2-carboxylic acid (**2b**) (89.0 mg, 0.700 mmol) and PPh_3 (0.55 g, 2.1 mmol) in pyridine/MeCN (1.0 ml) afforded after purification by chromatography on silica gel (PE / MTB 8 : 1, R_f = 0.17) 165 mg (0.430 mmol, 62%) of **3d** as a yellowish solid, mp 141°C. $[\alpha]_D^{20}$ –340 (*c* 5.2, $CHCl_3$). IR: 1/λ = 2916 (m), 1652 (vs), 1447 (m), 1432 (s), 1329 (m), 1277 (m), 1064 (m), 960 (m), 757 (m), 700 (vs) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34–1.45 (m, 1 H; CH*H*), 1.53–1.64 (m, 1 H; C*H*H), 2.03 (s, 3 H; CH_3), 2.66–2.70 (m, 2 H; SCH_2), 5.02 (dd, J = 10.3, 3.9 Hz, 1 H; H–4), 7.13 (dd, J = 4.9, 3.7 Hz, 1 H; th–H–4), 7.19–7.21 (m, 2 H; arom. H), 7.25–7.35 (m, 4 H; arom. H), 7.39–7.42 (m, 2 H; arom. H), 7.50 (dd, J = 5.1, 0.9 Hz, 1 H; th–H–5), 7.54–7.59 (m, 2 H; arom. H), 7.77 (dd, J = 3.6, 1.0 Hz, 1 H; th–H–3) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 15.60 (CH_3), 31.74 (CH_2), 33.73 (SCH_2), 73.61 (C–4), 92.98 (C–5), 126.46, 126.58, 127.58, 127.64 (each arom. CH), 128.00 (2 x arom. CH), 128.43, 130.02 (each arom. CH), 130.49 (th–C–2), 130.55 (arom. CH), 140.55, 143.81 (each arom. C), 157.97 (C–2)

ppm. MS (EI), m/z (%): 379 (M^+, 1), 331 (75), 305 (66), 182 (96), 165 (22), 136 (85), 111 (100), 61 (10). $C_{22}H_{21}NOS_2$ (379.53): Calcd. C, 69.62; H, 5.58; N, 3.69. Found: C, 69.36; H, 5.58; N, 3.74. Mol. mass calcd. 379.1065; found 379.1061 (M^+, HRMS).

(R)-(–)-4,5-Dihydro-4-(methylsulfanylmethyl)-2-(2-pyridyl)oxazole (4a). According to the procedure described for compound **3a** the conversion of amino alcohol **1a** (150 mg, 1.24 mmol), pyridine-2-carbonitrile (**2c**) (129 mg, 1.24 mmol) and $ZnCl_2$ (5.1 mg, 0.037 mmol) in chlorobenzene (2 ml) afforded after purification by chromatography on silica gel (MTB / CH_2Cl_2 2 : 1, R_f = 0.12) 93 mg (0.45 mmol, 36%) of **4a** as a colorless oil. $[\alpha]_D^{20}$ –5.1 (*c* 4.7, $CHCl_3$). IR: $1/\lambda$ = 3056 (w), 2975 (m), 2916 (m), 1639 (vs), 1581 (m), 1569 (m), 1469 (s), 1440 (s), 1363 (s), 1269 (m), 1247 (m), 1102 (s), 1081 (s), 1044 (s), 961 (s), 801 (m), 745 (s), 679 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.19 (s, 3 H; CH_3), 2.60–2.77 (m, 1 H; SCH*H*), 2.97–3.03 (m, 1 H; SC*H*H), 4.35–4.40 (m, 1 H; H–5), 4.55–4.66 (m, 2 H; H–4, H–5), 7.40 (ddd, *J* = 7.4, 4.7, 1.0 Hz, 1 H; py–H–5), 7.78 (td, *J* = 7.7, 1.6 Hz, 1 H; py–H–4), 8.01–8.06 (m, 1 H; py–H–3), 8.69–8.74 (m, 1 H; py–H–6) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 15.93 (CH_3), 38.95 (SCH_2), 66.42 (C–4), 72.55 (C–5), 123.80, 125.54, 136.51 (each py–CH), 146.36 (py–C–2), 149.65 (py–CH), 163.52 (C–2) ppm. MS (EI), m/z (%): 208 (M^+, 19), 183 (10), 162 (53), 147 (100), 134 (14), 123 (24), 119 (31), 106 (30), 92 (91), 78 (76), 61 (19), 56 (16), 51 (23). $C_{10}H_{12}N_2OS$ (208.28): Mol. mass calcd. 208.0670; found 208.0671 (M^+, HRMS).

(R)-(–)-4,5-Dihydro-5,5-diphenyl-4-(methylsulfanylmethyl)-2-(2-pyridyl)oxazole (4b). Under an atmosphere of argon conc. hydrochloric acid (ca. 20 mg) was added to a solution of amino alcohol **1b** (500 mg, 1.83 mmol) and **2d** (374 mg, 2.74 mmol) in dry chlorobenzene (3 ml). The mixture was stirred at 80°C for 24 h. All volatile materials were removed *in vacuo*, and the residue was chromatographed on silica gel (PE / MTB 1 : 1, R_f = 0.10) to give 430 mg (1.19 mmol, 65%) of **4b** as a yellow resin, which could not be crystallized. $[\alpha]_D^{20}$ –286 (*c* 13.0, $CHCl_3$). IR: $1/\lambda$ = 2914 (m), 1649 (m), 1493 (m), 1469 (m), 1440 (m), 1351 (s), 1124 (s), 975 (m), 758 (s), 745 (s), 699 (vs) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3 H; CH_3), 2.42 (dd, *J* = 13.7, 6.2 Hz, 1 H; SCH*H*), 2.51 (dd, *J* = 13.6, 7.4 Hz, 1 H; SC*H*H), 5.15 (dd, *J* = 7.4, 6.3 Hz, 1 H; H–4), 7.23–7.30 (m, 5 H; arom. H), 7.32–7.36 (m, 1 H; arom. H), 7.39–7.45 (m, 3 H; arom. H, py–H–5), 7.64–7.69 (m, 2 H; arom. H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1 H; py–H–4), 8.17 (d, *J* = 7.8 Hz, 1 H; py–H–3), 8.78–8.80 (m, 1 H; py–H–6) ppm. $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): δ 16.78 (CH_3), 37.84 (SCH_2), 75.65 (C–4), 93.77 (C–5), 124.17, 125.68, 126.70, 126.88, 127.73, 127.93, 128.07, 128.40, 136.60 (each arom. CH), 139.55, 143.51, 146.59 (each arom. C), 150.03 (py–C–6), 161.64 (C–2) ppm. MS (EI), m/z (%): 360 (M^+, 1), 313 (30), 238 (35), 163 (28), 131 (100), 105 (79), 78 (90), 69 (34). $C_{22}H_{20}N_2OS$ (360.47): Mol. mass calcd. 360.1296 found; 360.1291 (M^+, HRMS).

(S)-(–)-4,5-Dihydro-4-(methylsulfanylethyl)-2-(2-pyridyl)oxazole (4c). According to the procedure described for compound **4b** the conversion of amino alcohol **1c** (150 mg, 1.11 mmol) and **2d** (139 mg, 1.33 mmol) in chlorobenzene (1.5 ml) afforded after purification by chromatography on silica gel (MTB, R_f = 0.07) 136 mg (0.61 mmol, 55%) of **4c** as a yellowish oil.

$[\alpha]_D^{20}$ −120, $[\alpha]_{578}^{20}$ −127, $[\alpha]_{546}^{20}$ −147 (*c* 41.4, toluene) {ref. [40]: yield 61%, $[\alpha]_D^{20}$ −119.57, $[\alpha]_{578}^{20}$ −125.91, $[\alpha]_{546}^{20}$ −144.07 (*c* 52.4, toluene)}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.86–1.96 (m, 1 H; CH*H*), 1.99–2.08 (m, 1 H; C*H*H), 2.13 (s, 3 H; CH$_3$), 2.64–2.78 (m, 2 H; SCH$_2$), 4.14 (t, *J* = 8.1 Hz, 1 H; H–5), 4.45–4.54 (m, 1 H; H–4), 4.63 (dd, *J* = 8.3, 9.5 Hz, 1 H; H–5), 7.38–7.41 (m, 1 H; py–H–5), 7.76–7.80 (m, 1 H; py–H–4), 8.01–8.04 (m, 1 H; py–H–3), 8.70–8.72 (m, 1 H; py–H–6) ppm.

(S)-(−)-4,5-Dihydro-5,5-diphenyl-4-(methylsulfanylethyl)-2-(2-pyridyl)oxazole ***(4d)***. According to the procedure described for compound **4b** the conversion of amino alcohol **1d** (90 mg, 0.31 mmol) and **2d** (51 mg, 0.38 mmol) in chlorobenzene (1 ml) afforded after purification by chromatography on silica gel (PE / MTB 2 : 3, R_f = 0.15) 62 mg (0.17 mmol, 53%) of **4d** as a colorless solid, mp 99°C. $[\alpha]_D^{20}$ −374 (*c* 5.1, CHCl$_3$). IR: 1/λ = 2915 (m), 1650 (m), 1493 (m), 1469 (m), 1447 (m), 1439 (m), 1362 (m), 1341 (m), 1124 (m), 963 (m), 758 (m), 700 (s) cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.38–1.48 (m, 1 H; CH*H*), 1.56–1.65 (m, 1 H; C*H*H), 2.04 (s, 3 H; CH$_3$), 2.75–2.80 (m, 2 H; SCH$_2$), 5.14 (dd, *J* = 10.7, 3.6 Hz, 1 H; H–4), 7.17–7.20 (m, 2 H; arom. H), 7.23–7.30 (m, 3 H; arom. H), 7.32–7.37 (m, 1 H; arom. H), 7.39–7.46 (m, 3 H; arom. H, py–H–5), 7.58–7.62 (m, 2 H; arom. H), 7.83 (td, *J* = 7.7, 1.6 Hz, 1 H; py–H–4), 8.14 (dd, *J* = 7.9, 0.9 Hz, 1 H; py–H–3), 8.80 (dt, *J* = 4.2, 1.2 Hz, 1 H; py–H–6) ppm. ^{13}C{^{1}H} NMR (50 MHz, CDCl$_3$): δ 15.57 (CH$_3$), 31.93 (CH$_2$), 33.58 (CH$_2$), 73.89 (C–4), 93.34 (C–5), 124.03, 125.64, 126.58, 126.65, 127.61, 127.96, 128.06, 128.45, 136.72 (each arom. CH), 140.46, 143.74, 146.68 (each arom. C), 150.23 (py–C–6), 161.24 (C–2) ppm. MS (EI), m/z (%): 374 (M$^+$, 7), 326 (40), 300 (78), 268 (31), 194 (30), 177 (89), 165 (34), 131 (75), 105 (57), 84 (72), 78 (100). $C_{23}H_{22}N_2OS$ (374.50): Calcd. C, 73.77; H, 5.92; N, 7.48. Found C, 73.21; H, 6.12; N, 7.36. Mol. mass calcd. 374.1453; found 374.1455 (M$^+$, HRMS).

3.3 *Bis[(R)-4,5-dihydro-4-(methylsulfanylmethyl)-2-(2-thienyl)oxazole]copper(II) tetrafluoroborate (5)*

A solution of ligand **3a** (40 mg, 0.19 mmol) in absolute ethanol (1 ml) was added gradually to a stirred solution of $Cu(BF_4)_2 \cdot x\ H_2O$ (20% Cu) (32 mg, 0.090 mmol) in absolute ethanol (1.5 ml). The resulting dark-green solution was filtered through a pad of glass wool. The product crystallized by solvent diffusion between ethanol and hexane within 2 d as dark-green needles (49 mg, 0.070 mmol, 74%). The isolated crystals were suitable for a X-ray structure analysis. Mp 175°C (decomposition). IR (KBr): 1/λ = 1617 (s), 1531 (m), 1427 (m), 1392 (m), 1266 (m), 1224 (m), 1084 (vs), 1065 (vs), 957 (m), 729 (m) cm^{-1}. MS (FAB), m/z (%): 489 (M$^+$ − 2 BF$_4$, 33), 276 (32), 214 (100).

Crystal data and structure refinement for 5. $C_{18}H_{22}B_2CuF_8N_2O_2S_4$ (663.81); crystal dimensions: 0.5 x 0.5 x 0.3 mm^3; temperature: 298 K; wavelength: 0.71073 Å; crystal system: orthorhombic; space group: $P2_12_12_1$ (No. 19); unit cell dimensions: a = 11.622(2), b = 13.384(3), c = 19.837(4) Å, $\alpha = \beta = \gamma = 90°$, V = 3085.6(11) Å^3, Z = 4; density d_{calcd} = 1.429 g/cm^3; *m*(Mo-

K_α) = 10.3 cm^{-1}, θ range for data collection: 0.0° to 55.0°; scan type: ω; index ranges: $-17 < h < 17$, $-20 < k < 18$, $-30 < l < 22$; weighting scheme: $1/[\sigma^2 F_o^2 + (0.0884\,P)^2]$, $P = (\text{Max } F_o^2 + 2F_c^2) / 3$; no. of reflections collected: 6987; no. of independent reflections: 2855 [$I > 4.0\sigma(I)$]; parameters: 423; R indices: R1 = 0.0809, ωR2 = 0.2279; min. and max. resd. dens. (ε Å^3): 0.38, –0.47. The measurement was carried out on a Siemens SMART CCD diffractometer with a sealed tube. Preliminary cell constants were obtained from 45 frames (width of 0.3° in ω). Final cell constants were obtained by global refinements of reflections obtained from integration of all the frame data. A frame width of 0.3° in ω and a counting time of 30 s per frame at a crystal-to-detector distance of 3.0 cm was used. The collected frames were integrated using the preliminary cell-orientation matrix. The software SMART [50] was used for data collection and determination of lattice parameters, SAINT [51] for integration of intensity and scaling, SADABS [52] for absorption correction and SHELXTL [53] for data reduction, structure determination and refinement. The BF_4 groups are highly disordered.

3.4 Asymmetric catalysis: ethyl 2-(3-oxobutyl)cyclopentanone-2-carboxylate (9)

Metal salt **8** (0.013 mmol, 5 mol%), chiral ligand **3** or **4** (0.017 mmol, 7.5 mol%) and oxo-ester **6** (40 mg, 0.25 mmol) were dissolved in CH_2Cl_2 (0.5 ml). After stirring for 1 h at room temp. methyl vinyl ketone (**7**) (20 µl, 0.28 mmol) was added and the mixture was stirred for 16 h at room temp. Subsequently, the mixture was directly transferred on a SiO_2 column (3 cm) and the product was eluted with PE / MTB 1 : 1 (R_f = 0.25). The product mixture was analyzed by chiral GC, isotherm elution (130°C); enantiomers of **9**: t_R = 30.3 min and 32.4 min.

4. Acknowledgment

This work was supported by the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft and the Graduiertenkolleg "Metallkatalysatoren". We are also grateful to Prof. S. Blechert and the Institut für Organische Chemie der Technischen Universität Berlin for support. J. C. also thanks the Deutsche Forschungsgemeinschaft for a fellowship.

5. References

[1] Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.
[2] Ojima, I.; ed. *Catalytic Asymmetric Synthesis*, Weinheim, VCH, 1993.
[3] Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis with Transition Metal Compounds*, vol. 2, *Ligands*, Weinheim, VCH, 1993.
[4] Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894.
[5] Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815.
[6] Bolm, C. *Angew. Chem.* **1991**, *103*, 556–558; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 542–544.
[7] Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769–1772.

[8] Frost, C. G.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1993**, *4*, 1785–1788.
[9] Allen, J. V.; Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron* **1994**, *50*, 799–808.
[10] Brunner, H.; Haßler, B. *Z. Naturforsch. B* **1998**, *53b*, 476–480.
[11] Gladiali, S.; Pinna, L.; Delogu, G.; Graf, E.; Brunner, H. *Tetrahedron: Asymmetry* **1990**, *1*, 937–942.
[12] Brunner, H.; Störiko, R.; Nuber, B. *Tetrahedron: Asymmetry* **1998**, *9*, 407–422.
[13] Brunner, H.; Störiko, R.; Rominger, F. *Eur. J. Inorg. Chem.* **1998**, 771–781.
[14] Brunner, H.; Störiko, R. *Eur. J. Inorg. Chem.* **1998**, 783–788.
[15] Brunner, H.; Henrichs, C. *Tetrahedron: Asymmetry* **1995**, *6*, 653–656.
[16] Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1997**, *8*, 3183–3184.
[17] Brunner, H.; Brandl, P. *Tetrahedron: Asymmetry* **1991**, *2*, 919–930.
[18] Brunner, H.; Huber, C. *Z. Naturforsch. B* **1991**, *46b*, 1145–1148.
[19] Brunner, H.; Brandl, P. *J. Organomet. Chem.* **1990**, *390*, C81–C83.
[20] Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1–C3.
[21] Brunner, H.; Becker, R.; Riepl, G. *Organometallics* **1984**, *3*, 1354–1359.
[22] Augier, C.; Malara, L.; Lazzeri, V.; Waegell, B. *Tetrahedron Lett.* **1995**, *36*, 8775–8778.
[23] Review: Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259–1266.
[24] Christoffers, J. *Liebigs Ann./Recueil* **1997**, 1353–1358.
[25] Christoffers, J.; Rößler, U. *Tetrahedron: Asymmetry* **1998**, *9*, 2349–2357.
[26] End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem. Eur. J.* **1998**, *4*, 818–824.
[27] Fahrni, C. J.; Pfaltz, A. *Helv. Chim. Acta* **1998**, *81*, 491–524.
[28] DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1996**, *37*, 2633–2636.
[29] Nishiyama, H.; Yamaguchi, S.; Park, S.–B.; Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 43–150.
[30] Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846–848.
[31] Itsuno, S.; Hirao, A.; Nakahama, S.; Yamazaki, N. J. *Chem. Soc., Perkin Trans. 1* **1983**, 1673–1676.
[32] Desimoni, G.; Dusi, G.; Faita, G.; Quadrelli, P.; Righetti, P. *Tetrahedron* **1995**, *51*, 4131–4144.
[33] Grant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297–2360.
[34] Jnaneshwara, G. K.; Deshpande, V. H.; Latithambika, M.; Ravindranathan, T.; Bedekar, A. V. *Tetrahedron* Lett. **1998**, *39*, 459–462.
[35] Zhou, P.; Blubaum, J. E.; Burns, C. T.; Natale, N. R. *Tetrahedron Lett.* **1997**, *38*, 7019–7020.
[36] Clarke, D. S.; Wood, R. *Synth. Commun.* **1996**, *26*, 1335–1340.
[37] Witte, H.; Seeliger, W. *Liebigs Ann. Chem.* **1974**, 996–1009.
[38] Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353–9372.
[39] Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 412–418.
[40] Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499–507.
[41] Brunner, H.; Obermann, U.; Wimmer, P. *Organometallics* **1989**, *8*, 821–826.
[42] Yamada, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666–3672.
[43] Review: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem.* **1997**, *109*, 1290–1311; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236–1256.
[44] Brunner, H.; Hammer, B. *Angew. Chem.* **1984**, *96*, 305–306; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 312–313.
[45] Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 593–596.
[46] Review: Leonard, J.; Diez–Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051–2061.
[47] Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 4057–4060.
[48] Sasai, H.; Emori, E.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 5561–5564.
[49] Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141–3149.
[50] SMART: Software Reference Manual.; Version 4.0, Siemens Analytical X–Ray Instruments, Madison (WI), 1996.
[51] SAINT: Software Reference Manual, Version 4.0, Siemens Analytical X–Ray Instruments, Madison (WI) 1994; 1996.
[52] Sheldrick, G. M. SADABS: Empirical Absorption Correction Program, Göttingen 1996.
[53] Sheldrick, G. M. SHELXTL: Version 4.0, Siemens Analytical X–Ray Instruments, Madison (WI) 1995.