Enantioselective Catalyses; 126:[1] Axially Chiral *N,N*-Ligands with Binaphthyl/Bipyridyl Structure

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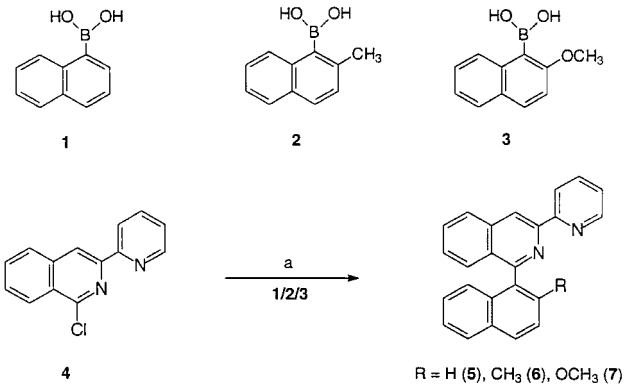
Abstract: *N,N*-Ligands with combined binaphthyl/bipyridyl structure were synthesized by palladium-catalyzed coupling of 1-naphthylboronic acids with 1-halogenoisoquinoline derivates and with 4-bromo-2-(2-pyridyl)naphtho[2,3-*d*]-1,3-oxazole. Racemic 1-(2-methoxy-1-naphthyl)-3-(2-pyridyl)isoquinoline was resolved via diastereomeric salt formation with (–)-3-bromocamphor-8-sulfonic acid and the absolute configuration was determined by X-ray analysis.

Key words: binaphthyl, bipyridyl, Suzuki coupling, axial chirality, absolute configuration

Phosphanes used to be the favorite ligand components of enantioselective catalytic systems for a long time. However, recently there was a renaissance of nitrogen ligands in enantioselective catalysis.[2] Bipyridyl ligands, known for their excellent coordination behaviour, are available in a wide variety including enantiomeric purity,[3] but bipyridyl ligands with axial chirality are rare. As ligands, possessing both the coordination properties of bipyridyls and the flexible element of axial chirality, appeared to be promising for enantioselective catalysis, compounds of these type have been synthesized.

In the present paper the synthesis of members of three types of axially chiral *N,N*-ligands with binaphthyl/bipyridyl structure is described.[4] These are 1-naphthyl-3-(2-pyridyl)isoquinolines **5–7** with hydrogen, methyl and methoxy groups, respectively, in 2-position of the naphthalene ring, 1,1'-bis(2-methoxy-1-naphthyl)-3,3-biisoquinoline (**11**) and 4-(2-methoxy-1-naphthyl)-2-(2-pyridyl)naphtho[2,3-*d*]-1,3-oxazole (**16**). Recently, the synthesis of **7** and **11** has been described.[5] We present alternative routes to these compounds and in addition we report on the resolution and the absolute configuration of **7**. The first step in the synthesis of the binaphthyl/biypridyl ligands was the formation of the 1-naphthylboronic acids, required for the Suzuki-type coupling.[6] The boronic acids used were 1-naphthylboronic acid (**1**), 2-methyl-1-naphthylboronic acid (**2**) and 2-methoxy-1-naphthylboronic acid (**3**) (Scheme 1). They were prepared from the corresponding 1-bromo-naphthalenes via conversion into Grignard compounds and subsequent reaction with trimethylborate.[7] 1-Bromo-2-methylnaphthalene had been prepared by bromination of 2-methylnaphthalene.[8] 1-Bromo-2-methoxynaphthalene has been synthesized by bromination of 2-hydroxynaphthalene and methylation of the product with dimethylsulfate.[9,10]

The synthesis of 1-chloro-3-(2-pyridyl)isoquinoline (**4**) started with a condensation of pyridene-2-carbonitrile with ortho-tolunitrile in liquid ammonia/potassium amide.[11] The resulting 1-amino-3-(2-pyridyl)isoquinoline was diazotized with sodium nitrite yielding 1-hydroxy-3-(2-pyridyl)isoquinoline after acidic hydrolysis. After reaction with $POCl_3$ **4** could be isolated.[12]

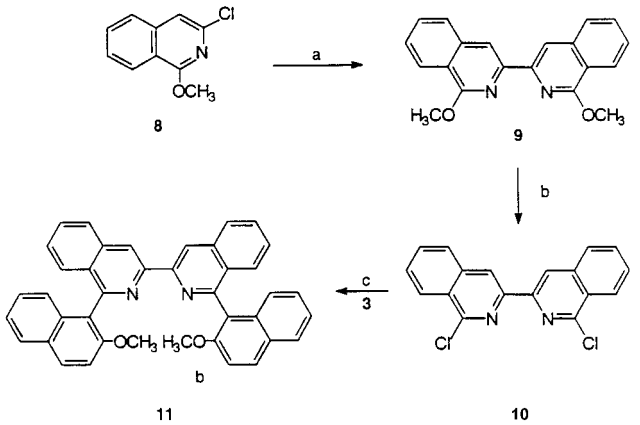


Reagents and conditions: a) $(Ph_3P)_4Pd$ (3 mol %)/2 M aq Na_2CO_3/ethylene glycol dimethyl ether, reflux, 16 h; 5: 75%; 6: 71%; 7: 71%

Scheme 1

Starting material for the synthesis of 1,1'-dichloro-3,3'-biisoquinoline (**10**) (Scheme 2) was phthalide. Ring opening with potassium cyanide gave 2-cyanomethylbenzoic acid,[13] which was treated with $PCl_5/POCl_3$ to undergo ring closure resulting in 1,3-dichloroisoquinoline.[14] Taking advantage of the different reactivity of the chloro substituents of 1,3-dichloroisoquinoline, the more labile chloro atom in 1-position of the isoquinoline system was replaced by a methoxy group in a reaction with sodium methanolate in methanol yielding 1-chloro-3-methoxyisoquinoline (**8**).[15] A nickel-catalyzed reductive coupling of **8** afforded the C_2-symmetric 1,1'-dimethoxy-3,3'-biisoquinoline (**9**).[16,17] Boiling of **9** in $POCl_3$ resulted in the substitution of the two methoxy groups by chlorine atoms to give **10** providing suitable sites for a subsequent Suzuki coupling.

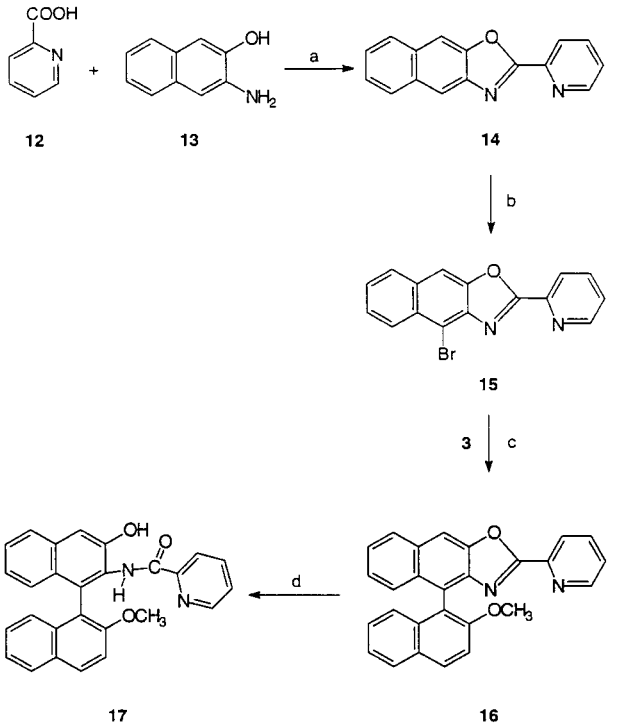
4-Bromo-2-(2-pyridyl)naphtho[2,3-*d*]-1,3-oxazole (**15**) (Scheme 3) was prepared starting from 2,3-dihydroxynaphthalene which was converted to 2-amino-3-hydroxynaphthalene (**13**) by an autoclave reaction with 32% aqueous ammonia.[18] The product was treated with pyridine-2-carboxylic acid (**12**) in polyphosphoric acid to yield



Reagents and conditions: a) NaH/*t*-BuOH/Ph_3P/anhyd $Ni(OAc)_2$/ethylene glycol dimethyl ether, 3.5 h, 67%; b) $POCl_3$, reflux, 36 h, 91%; c) $(Ph_3P)_4Pd$ (6 mol %)/ethylene glycol dimethyl ether/2 M aq Na_2CO_3, reflux, 36 h, 42%

Scheme 2

2-(2-pyridyl)naphtho[2,3-*d*]-1,3-oxazole (**14**).[19] To provide a coupling site, a halogene atom had to be introduced into the naphthalene ring. Our aim was to obtain a biaryl ligand, in which the oxazole nitrogen was located at the "inner" side of the biaryl system neighbouring the biaryl axis. Thus, in metal complexes the metal center should be as near to the biaryl axis as possible. According to the mesomeric formulas bromination of **14** should take place in ortho-position to the oxazole nitrogen atom, at least as long as the oxazole nitrogen was not protonated. Therefore, sodium carbonate was added as additional component in the bromination reaction of **14** in order to prevent protonation of the nitrogen by evolving HBr leading to the monobrominated product **15**.



Reagents and conditions: a) polyphosphoric acid, 170 °C, 2 h, 52%; b) $Br_2/CH_2Cl_2/Na_2CO_3/FeCl_3$ (cat.), 0 °C to r.t., 72%; c) $(Ph_3P)_4Pd$ (3 mol %)/ethylene glycol dimethyl ether/ 2 M aq Na_2CO_3, reflux, 16 h, 73%; d) KOH/MeOH, reflux, 90 min, 80%

Scheme 3

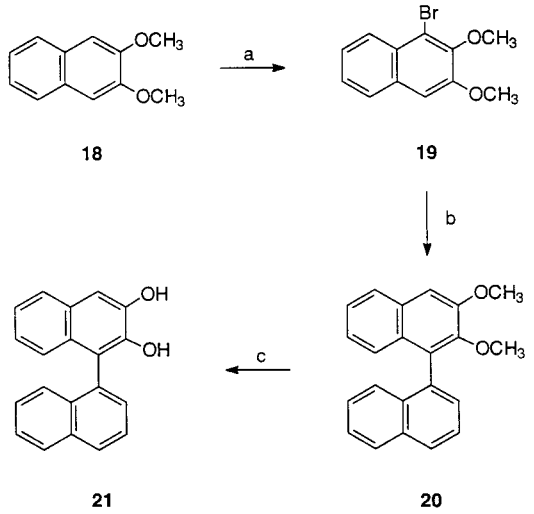
As it was not possible to determine the bromination position, neither from the NMR-spectra of **15** nor from its derivative **16**, which was prepared afterwards, **16** was subjected to partial hydrolysis resulting in 3-hydroxy-2'-methoxy-2-(2-pyridylcarbonyl)amino-1,1'-binaphthyl (**17**). NOESY experiments with **17** showed, that the N-bonded hydrogen of the (2-pyridylcarbonyl)amino group is in the vicinity of the methoxy group, proving that the bromination, as well as the coupling reaction resulting in **16** must have taken place at the "nitrogen-side" of the oxazole.

1-Naphthyl-3-(2-pyridyl)isoquinoline (**5**), 1-(2-methylnaphthyl)-3-(2-pyridyl)isoquinoline (**6**) and 1-(2-methoxynaphthyl)-3-(2-pyridyl)isoquinoline (**7**) were synthesized by Suzuki coupling[7] of the chloro derivative **4** and the boronic acids **1-3** according to Scheme 1 using 3 mol% of tetrakis(triphenylphosphane)palladium(0) [20] as the catalyst.

Double Suzuki coupling of **10** with **3** using 6 mol% of the Pd-catalyst yielded 1,1'-bis(2-methoxy-1-naphthyl)-3,3'-biisoquinoline (**11**) as a mixture of the diastereomers (R_a),(R_a)/ (S_a),(S_a) and (R_a),(S_a)/(S_a),(R_a), which differ in the mutual orientation of their naphthyl substituents (Scheme 2). The diastereomer composition was determined by ^{1}H NMR (250 MHz, $CDCl_3$/DMSO-d_6). Integration of the signals of the methoxy groups at 3.81 and 3.83 ppm gave a diastereomer ratio of 1:1.

It was planned to synthesize *rac*-4-(2-methoxy-1-naphthyl)-2-(2-pyridyl)naphtho[2,3-*d*]-1,3-oxazole (**16**) via Grignard cross coupling of 1-bromo-2-methoxynaphthalene and 1-bromo-2,3-dimethoxynaphthalene. Introduction of an amino function in the 2-position and subsequent condensation with pyridene-2-carboxylic acid was supposed to give **16**. Thus, 2,3-dihydroxynaphthalene was dimethylated with dimethylsulfate and sodium hydroxide leading to 2,3-dimethoxynaphthalene (**18**) in high yield.[10] Compound **18** could be selectively monobrominated in the 1-position to 1-bromo-2,3-dimethoxynaphthalene (**19**). Subsequent Grignard cross coupling[21] with the model compound 1-bromonaphthalene using the catalyst $Ni(PPh_3)_2Cl_2$[22] resulted in 2,3-dimethoxy-1,1'-binaphthyl (**20**). Cleavage of the methoxy groups with BBr_3 in dry methylene chloride at –78 °C led to 2,3-dihydroxy-1,1'-binaphthyl (**21**) (Scheme 4).[23] However, neither the OCH_3 groups of 2,3-dimethoxy-1,1'-binaphthyl (**20**) nor the OH groups of 2,3-dihydroxy-1,1'-binaphthyl (**21**) could be replaced by the NH_2 substituent. Therefore, *rac*-4-(2-methoxy-1-naphthyl)-2-(2-pyridyl)naphtho[2,3-*d*]-1,3-oxazole (**16**) was synthesized by Suzuki coupling of the bromo compound **15** with the boronic acid **3**, which gave **16** in good yields (Scheme 3).

The isoquinoline **7** seemed to be most suitable for optical resolution. On the one hand the steric hindrance of the



Reagents and conditions: a) Br_2/CH_2Cl_2, 0 °C to r.t., 86%; b) $(Ph_3P)_2NiCl_2$ (2 mol %)/1-bromonaphthalene/Mg/THF, 16 h, r.t., 1 h, reflux; c) BBr_3/CH_2Cl_2, –78 °C, 84%

Scheme 4

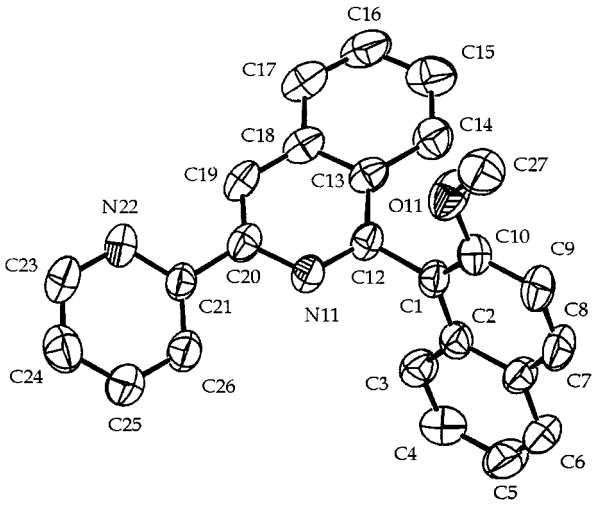


Figure. Ortep plot of the molecular structure of **7**. H atoms are omitted for clarity. Torsion angle C13-C12-C1-C2 = 107.2°, torsion angle C19-C20-C21-C26 = 163.1°. Bond lengths along the biaryl axes: 1.51 Å for C1-C12 and 1.49 Å for C20-C21.

methoxy group should be big enough to form sufficiently stable enantiomers, contrary to the unsubstituted 1-(1-naphthyl)-3-(2-pyridyl)isoquinoline (**5**). On the other hand **7** allowed a convenient enantiomer analysis by ^{1}H NMR spectroscopy. Addition of a four-fold molar excess of Pirkle's alcohol (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol led to a complete separation of the signals of the enantiomers in the 400 MHz ^{1}H NMR spectrum. In contrast 1-(2-methyl-1-naphthyl)-3-(2-pyridyl)isoquinoline (**6**) gave partially overlapping signals in the ^{1}H NMR spectrum even with a twenty-fold excess of the anthryl alcohol.

For optical resolution **7** was transformed into its dihydrochloride. Then an equimolar amount of the ammonium salt of (–)-3-bromocamphor-8-sulfonic acid was added. After crystallization two different substances had formed. One was pale yellow and crystalline, the other was dark yellow and amorphous, obviously the two diastereomeric salts, which differed considerably in their solubility in methanol. A solution of the less soluble fraction was eluted with methanol over a strongly basic ion exchange column to liberate the free base. NMR analysis after addition of Pirkle's alcohol revealed, that the (+)-enantiomer had been accumulated to an enantiomeric excess of 40–60%. Recrystallization led to a solid of nearly racemic composition, while the mother liquor contained the (+)-enantiomer with 94%ee. Repetition of the crystallization process increased the enantiomeric excess to > 96%. The (–)-enantiomer could be obtained by analogous work up of the solutions of the first step of the resolution process enriched in the (–)-enantiomer.

Crystallization from methylene chloride/petroleum ether (bp 40–60 °C) at –25 °C gave single crystals, which were suitable for X-ray analysis. The absolute configuration of the (+)-enantiomer of **7** (Figure) obtained from the Friedel pairs was determined to be (R_a), according to the rules given in Ref. 24.

The (+)-enantiomer of **7** was submitted to a racemization experiment. From the polarimetrically observed racemization in methylene chloride at 84.2 °C a racemization barrier of 113 kJ/mol (± 4 kJ/mol) was calculated, which is about 35 kJ/mol higher than that of unsubstituted 1-(1-naphthyl)isoquinoline.[25]

Solvents were dried and degassed according to standard procedures and stored under N_2. Petroleum ether used had bp 40–60 °C. Chromatography: Silica gel 60 (65–200 μm, Merck). TLC: Merck silica gel 60 F_{254} plates (visualization with UV light). Melting points: SMP-20 (Büchi), not corrected. IR: Beckman spectrometer IR 4240 (KBr). MS: MAT 311 A (EI) and MAT 95 (FD) (Finnigan). Intensities relative to the base peak (I = 100%). Optical rotations: Perkin-Elmer 241 polarimeter (1 dm cells at r.t.). Elemental analyses: Mikroanalytisches Labor of the University of Regensburg.

^{1}H NMR: AC 250 (250 MHz, Bruker) and ARX 400 (400 MHz, Bruker) (internal TMS). ^{13}C NMR (including DEPT sequences): AC 250 (63 MHz) and ARX 400 (100 MHz). Peak assignments: COSY and NOESY experiments. X-ray structure analysis of **7**: Anorganisch-Chemisches Institut of the University of Heidelberg. Protons in the NMR spectra of the different compounds have been labeled according to standard nomenclature of the subsystems naphthalene, isoquinoline and pyridine, adding the prefixes *naphth*, *isoquin* and *py*. In the coupled oxazole systems a distinction between the two naphthalene systems has been made by assigning the prefix *oxnaphth* to the naphthalene system carrying the oxazole ring.

1-(1-Naphthyl)-3-(2-pyridyl)isoquinoline (5); Typical Procedure

Under nitrogen protection the isoquinoline **4** (5.0 g, 20.8 mmol) and $(Ph_3P)_4Pd$ (718 mg, 0.62 mmol) were dissolved in ethylene glycol dimethyl ether (50 mL) and stirred for 10 min. A solution of **1** (3.57 g, 20.8 mmol) in EtOH (10 mL) and a 2 M Na_2CO_3 solution (20.8 mL, 41.6 mmol) was added and the mixture was refluxed for 16 h. The mixture was decanted and the residue was washed with CH_2Cl_2 until the yellow colour had disappeared. The combined organic phases were washed with brine (2 × 50 mL). The solution was dried (Na_2SO_4), filtered and the solvent was removed. Recrystallization from CH_2Cl_2/petroleum ether (1:1) resulted in a nearly colourless, microcrystalline powder; yield: 5.18 g (75%); mp 199 °C.

IR (KBr): ν = 3050 (C–H arom), 1620 (C=N), 1560 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27 (ddd, 1 H, $J_{5,4}$ = 7.6, $J_{5,6}$ = 4.8, $J_{5,3}$ = 1.0 Hz, py-H5), 7.33 (ddd, 1 H, J = 8.4, 6.9, 1.3 Hz), 7.38 (ddd, 1 H, J = 8.4, 7.0, 1.2 Hz), 7.49 (ddd, 1 H, J = 8.2, 6.9, 1.2 Hz), 7.53 (dd, 1 H, J = 8.5, 0.8 Hz), 7.60–7.70 (m, 4 H), 7.74 (ddd, 1 H, $J_{4,5} \approx J_{4,3}$ = 7.6, $J_{4,6}$ = 1.8 Hz, py-H4), 7.96 (d, 1 H, J = 8.2 Hz), 8.01 (dd, 1 H, J = 6.4, 2.7 Hz), 8.05 (d, 1 H, J = 8.3 Hz, isoquin-H5), 8.53 (ddd, 1 H, $J_{3,4}$ = 8.0, $J_{3,5} \approx J_{3,6}$ = 1.0 Hz, py-H3), 8.74 (ddd, 1 H, $J_{6,5}$ = 4.8, $J_{6,4}$ = 1.8, $J_{6,3}$ = 1.0 Hz, py-H6), 8.90 (d, 1 H, J_{45} = 0.7 Hz, isoquin-H4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 117.2, 121.7, 123.3, 125.2, 125.9, 126.2, 126.2, 127.4, 127.7, 127.8, 128.1, 128.2, 128.3 (quart C), 128.8, 130.3, 132.4 (quart C), 133.7 (quart C), 136.9, 137.2 (quart C), 137.3 (quart C), 149.0 (quart C), 149.2 (quart C), 156.6 (quart C), 159.9.

MS (EI, 70 eV): *m/z* (%) = 332 (77, M^+), 331 (100, $[M–H]^+$).

Anal. calcd for $C_{24}H_{16}N_2$ (332.4): C 86.72, H 4.85, N 8.43; found: C 86.55, H 4.81, N 8.37.

***rac*-1-(2-Methyl-1-naphthyl)-3-(2-pyridyl)isoquinoline (6)**

The synthesis was carried out analogous to the preparation of **5**, using **4** (3.88 g, 16.1 mmol), $(Ph_3P)_4Pd$ (550 mg, 0.48 mmol), ethylene glycol dimethyl ether (40 mL), **2** (3.00 g, 16.1 mmol) and a 2 M Na_2CO_3 solution (16.1 mL, 32.2 mmol); yield: 3.97 g (71%); mp 158 °C.

IR (KBr): ν = 3050, 3010 (C–H arom), 2950, 2910 (C–H aliph), 1620 (C=N), 1580, 1565 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.16 (s, 3 H, CH_3), 7.11 (d, 1 H, J = 8.5 Hz), 7.22–7.26 (m, 1 H), 7.29 (ddd, 1 H, J = 7.5, 4.8, 1.2 Hz), 7.37–7.43 (m, 3 H), 7.52 (d, 1 H, J = 8.4 Hz), 7.66–7.70 (m, 1 H), 7.75 (ddd, 1 H, $J \approx J'$ = 7.7, J = 1.8 Hz), 7.91 (d, 1 H, J = 8.2 Hz), 7.94 (d, 1 H, J = 8.5 Hz), 8.07 (d, 1 H, J = 8.3 Hz, isoquin-H5), 8.50 (ddd, 1 H, J = 8.0, $J \approx J_{3,6}$ = 1.0 Hz, py-H3), 8.75 (ddd, 1 H, J = 4.8, 1.8, $J_{6,3}$ = 1.0 Hz, py-H6), 8.89 (s, 1 H, isoquin-H4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.2 (CH_3), 117.1, 121.9, 123.2, 125.0, 125.9, 126.2, 127.2, 127.7, 127.9, 128.2, 128.4, 128.5 (quart C), 128.8, 130.4, 132.1 (quart C), 133.0 (quart C), 134.4 (quart C), 135.2 (quart C), 136.9, 137.2 (quart C), 149.2, 149.6 (quart C), 156.8 (quart C), 160.0 (quart C).

MS (EI, 70 eV): *m/z* (%) = 346 (67, M^+), 345 (100, $[M–H]^+$).

Anal. calcd for $C_{25}H_{18}N_2$ (346.4): C 86.68, H 5.24, N 8.09; found: C 86.79, H 5.22, N 8.01.

***rac*-1-(2-Methoxy-1-naphthyl)-3-(2-pyridyl)isoquinoline (7)**

The synthesis was carried out analogously to the synthesis of **5**, starting from **4** (5.36 g, 22.3 mmol), $(Ph_3P)_4Pd$ (825 mg, 0.71 mmol), ethylene glycol dimethyl ether (60 mL), **3** (4.50 g, 22.3 mmol) and a 2 M Na_2CO_3 solution (22.3 mL, 44.6 mmol); yield: 5.71 g (15.8 mmol, 71%); mp 156 °C. Spectroscopic data given in ref. 5 have been confirmed.

MS (EI, 70 eV): *m/z* (%) = 362 (100, M^+).

Anal. calcd for $C_{25}H_{18}N_2O$ (362.4): C 82.85, H 5.00, N 7.73; found: C 82.79, H 4.99, N 7.59.

1,1'-Dimethoxy-3,3'-biisoquinoline (9)

Under nitrogen protection *tert*-butyl alcohol (3.82 g, 51.5 mmol) was added dropwise to a suspension of NaH (3.72 g, 155 mmol), anhyd $NiAc_2$ (4.56 g, 25.8 mmol) and Ph_3P (24.6 g, 93.8 mmol) in ethylene glycol dimethyl ether (90 mL). The reaction mixture was kept at 65 °C for 2 h. Then a solution of **8** (5.00 g, 25.8 mmol) in ethylene glycol dimethyl ether (30 mL) was added and the mixture was stirred at 65 °C for 3.5 h. After cooling, excess NaH was cautiously hydrolized with EtOH. The solvent was removed and the oily residue was dissolved in CH_2Cl_2. The solution was then filtered with CH_2Cl_2 through a silica gel column (5 cm) and the solvent was evaporated. To remove the excess of Ph_3P the residue was washed with petroleum ether until TLC analysis did not show any residual Ph_3P. The nearly colourless product was recrystallized from acetone/petroleum ether at –25 °C; yield: 2.74 g (67%); mp 219 °C.

IR (KBr): ν = 2980, 2960, 2890, 2850 (C–H aliph), 1625 (C=N), 1575s cm^{-1} (C=C).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 4.30 (s, 6 H, OCH_3), 7.51 (ddd, 2 H, J = 8.2, 7.0, 1.2 Hz), 7.65 (ddd, 2 H, J = 8.2, 7.0, 1.3 Hz), 7.87 (d, 2 H, J = 8.2 Hz), 8.25 (d, 2 H, J = 8.2 Hz), 8.42 (s, 2 H, H-4,4').

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 53.6 (OCH_3), 111.7, 119.9 (quart C), 124.2, 126.5, 127.2, 130.4, 138.9 (quart C), 147.2 (quart C), 160.3 (quart C).

MS (EI, 70 eV): *m/z* (%) = 316 (100, M^+).

Anal. calcd for $C_{20}H_{16}N_2O_2$ (316.4): C 75.93, H 5.10, N 8.86; found: C 75.83, H 5.25, N 8.68.

1,1'-Dichloro-3,3'-biisoquinoline (10)

Under exclusion of moisture the compound **9** (300 mg, 0.95 mmol) was suspended in $POCl_3$ and the mixture was refluxed for 36 h. The hot solution was poured onto ice and the mixture was brought to a pH of 10 with solid NaOH, causing precipitation. The precipitate was filtered, washed with H_2O and dried in vacuo over solid KOH. Recrystallization from $CHCl_3$ resulted in a colourless powder; yield: 280 mg (91%); mp >250 °C.

IR (KBr): ν = 3050 (C–H arom), 1625 (C=N), 1575, 1565 (C=C).

MS (EI, 70 eV): *m/z* (%) = 324 (100, M^+) rel. to ^{79}Br.

Anal. calcd for $C_{18}H_{10}Cl_2N_2$ (325.2): C 66.48, H 3.10, N 8.61; found: C 66.64, H 3.22, N 8.37.

1,1'-Bis(2-methoxy-1-naphthyl)-3,3'-biisoquinoline (11)

The synthesis of **11** was carried out analogous to the preparation of **5**, starting from **10** (150 mg, 0.46 mmol), $(Ph_3P)_4Pd$ (32 mg, 0.028 mmol), ethylene glycol dimethyl ether (8 mL), boronic acid **3** (186 mg, 0.92 mmol) and a 2 M Na_2CO_3 solution (1 mL, 2 mmol). Reaction time was 36 h; yield: 136 mg (52%); mp > 250 °C. Spectroscopic data given in ref. 5 have been confirmed.

MS (EI, 70 eV): *m/z* (%) = 568 (49, M^+), 553 (100, $[M–CH_3]^+$).

Anal. calcd for $C_{40}H_{28}N_2O_2$ (568.7): C 84.48, H 4.96, N 4.93; found: C 84.77, H 5.12, N 4.99.

1-Bromo-2,3-dimethoxynaphthalene (19)

To a stirred solution of **18** (5.00 g, 26.6 mmol) in CH_2Cl_2 (50 mL), protected from light and cooled to 0 °C, was added slowly a solution of Br_2 (4.25 g, 26.6 mmol) in CH_2Cl_2 (30 mL) and the stirring was continued for 30 min. The dark brown reaction mixture was allowed to warm to r.t. and washed with satd $NaHCO_3$ solution (3 × 20 mL) and H_2O (3 × 20 mL). The organic phase was dried (Na_2SO_4). After the solvent was removed, the residue was dissolved in toluene and filtered through silica gel. The solvent was evaporated and the residue was recrystallized from petroleum ether/Et_2O (2:1); yield: 6.11 g (86%); mp 49 °C.

IR (KBr): ν = 3050, 3000 (C–H arom), 2960, 2930, 2860, 2830 (C–H aliph), 1600, 1565, 1495 cm^{-1} (C=C).

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.95 (s, 3 H, C3-OCH_3), 3.97 (s, 3 H, C2-OCH_3), 7.13 (s, 1 H, H-4), 7.38–7.47 (m, 2 H), 7.64–7.71 (m, 1 H), 8.10–8.17 (m, 1 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 55.9 (OCH_3), 60.7 (OCH_3), 107.1, 116.4 (quart C), 125.1, 126.0, 126.7, 126.7, 128.0 (quart C), 131.6 (quart C), 147.4 (quart C), 152.6 (quart C).

MS (EI, 70 eV): *m/z* (%) = 266 (100, M^+) ref. to ^{79}Br.

Anal. calcd for $C_{12}H_{11}BrO_2$ (267.1): C 53.96, H 4.15; found: C 54.04, H 4.38.

rac-2,3-Dimethoxy-1,1'-binaphthyl (20)

Under nitrogen protection Mg turnings (7.5 g, 309 mmol) were suspended in part of a solution of 1-bromonaphthalene (51.2 g, 247 mmol) in THF (180 mL). The Grignard reaction was started by heating the reaction mixture. The rest of the solution was added dropwise, keeping the mixture at slight reflux. Then the reaction mixture was refluxed for 1 h. The Grignard solution was filtered through glass wool and added dropwise to a solution of **19** (60.0 g, 225 mmol) and $(Ph_3P)_2NiCl_2$ (3.0 g, 4.59 mmol) in THF (120 mL). The mixture was stirred for 16 h at r.t. and then refluxed for 1 h. Excess Grignard reagent was hydrolized by the addition of 2 M HCl (300 mL) and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with satd $NaHCO_3$ solution (3 × 40 mL), 20% $Na_2S_2O_3$ solution (3 × 40 mL) and H_2O (3 × 40 mL). The organic phase was dried (Na_2SO_4) and filtered through silica gel. The filtrate was concentrated and addition of Et_2O led to the precipitation of a colourless solid. The product was filtered, dried in vacuo and crystallized from CH_2Cl_2/petroleum ether at –25 °C; yield: 39.8 g (56%); mp 175 °C.

IR (KBr): ν = 3060, 3010 (C–H arom), 2960 (C–H aliph,); 1585, 1510 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.53 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 7.05–7.14 (m, 2 H), 7.27 (ddd, 1 H, *J* = 8.4, 6.8, 1.3 Hz), 7.30 (s, 1 H, OCH_3-naphth-H4), 7.34–7.38 (m, 2 H), 7.41–7.47 (m, 2 H), 7.60 (dd, 1 H, *J* =7.0, 5.7 Hz), 7.78 (d, 1 H, *J* = 8.2 Hz), 7.92–7.96 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.7 (OCH_3), 61.0 (OCH_3), 107.0, 124.0, 125.2, 125.3, 125.7, 126.0, 126.0, 126.3, 126.5, 127.9, 128.1, 128.1, 129.2 (quart C), 130.1 (quart C), 131.1 (quart C), 132.9 (quart C), 133.6 (quart C), 134.0 (quart C), 147.2 (quart C), 152.2 (quart C).

MS (EI, 70 eV): *m/z* (%) = 314 (100, M^+).

Anal. calcd for $C_{22}H_{18}O_2$ (314.4): C 84.05, H 5.77; found: C 83.78, H 5.61.

rac-2,3-Dihydroxy-1,1'-binaphthyl (21)

Under nitrogen protection *rac*-**20** (5.00 g,15.9 mmol) was dissolved in CH_2Cl_2 (150 mL) and the solution was cooled to –78 °C. A cooled (–78 °C) solution of BBr_3 (19.9 g, 79.4 mmol) in CH_2Cl_2 (150 mL) was slowly added and the mixture was stirred for 1 h at –78 °C. The mixture was allowed to warm to r.t. Excess BBr_3 was hydrolized by cautious addition of MeOH (100 mL) followed by stirring for 1 h. The solution was washed with satd $NaHCO_3$ solution (3 × 100 mL) and dried (Na_2SO_4). The solvent was removed and the residue was chromatographed on silica gel with petroleum ether/acetone (7:1). Evaporation of the solid yielded a colourless powder; yield: 3.84 g (84%); mp 186 °C; R_f (silica gel, petroleum ether/acetone, 7:1) 0.04.

IR (KBr): ν = 3100–3560 (O–H), 3050, 3040 (C–H arom), 1590, 1580, 1515 cm^{-1} (C=C).

^1H NMR (DMSO-d_6, 250 MHz): δ = 6.80 (d, 1 H, *J* = 8.4 Hz), 6.99 (ddd, 1 H, *J* = 8.4, 6.8, 1.4 Hz), 7.18 (ddd, 1 H, *J* = 8.1, 6.8, 1.4 Hz), 7.22 (d, 1 H, *J* = 8.5 Hz), 7.30 (s, 1 H, OH-naphth-H4), 7.31 (ddd, 1 H, *J* = 8.5, 6.7, 1.3 Hz), 7.38 (dd, 1 H, *J* = 7.0, 1.3 Hz), 7.49 (ddd, 1 H, *J* = 8.2, 6.6, 1.4 Hz), 7.64 (dd, 1 H, *J* = 8.2, 7.1 Hz), 7.69 (md, 1 H, *J* = 8.1 Hz), 8.00 (2 d, 2 H, *J* = 8.2, 8.3 Hz), 8.65 (br s, 1 H, OH), 10.26 (br s, 1 H, OH).

^{13}C NMR (DMSO-d_6, 63 MHz): δ = 109.0, 119.8 (quart C), 122.9, 123.0, 124.0, 125.7, 125.7, 125.8, 125.9, 127.4, 128.1, 128.4, 128.6 (quart C), 128.7 (quart C), 132.4 (quart C), 133.4 (quart C), 134.5 (quart C), 144.4 (quart C), 146.1 (quart C).

MS (EI, 70 eV): *m/z* (%) = 286 (100, M^+).

Anal. calcd for $C_{20}H_{14}O_2$ (286.3): C 83.90, H 4.93; found: C 83.81, H 4.92.

2-(2-Pyridyl)naphtho[2,3-*d*]-1,3-oxazole (14)

A mixture of **13** (3.0 g, 18.8 mmol) and **12** (2.32 g, 18.8 mmol) was heated in polyphosphoric acid (30 mL) to 170 °C for 2 h and then poured onto ice. The aqueous suspension was extracted with $CHCl_3$ (3 × 100 mL). The combined organic phases were washed with H_2O several times and dried (Na_2SO_4). The green-brown product was chromatographed on silica gel with CH_2Cl_2/acetone (50:1). After removing the solvent the residue was recrystallized from CH_2Cl_2/pentane; yield: 2.42 g (52%); mp 198–199 °C; R_f (silica gel, CH_2Cl_2/acetone, 50:1) 0.30.

IR (KBr): ν = 3090, 3060, 3000 (C–H arom), 1640, 1615 (C=N), 1590, 1560, 1505 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.45–7.55 (m, 3 H), 7.92 (ddd, 1 H, $J_{4,3}$ = 7.9, $J_{4,5}$ = 7.6, $J_{4,6}$ = 1.7 Hz, py-H4), 7.96–8.03 (m, 2 H), 8.04 (s, 1 H, naphth-H1), 8.28 (s, 1 H, naphth-H4), 8.44 (ddd, 1 H, $J_{3,4}$ = 7.9, $J_{3,5}$ = 1.2, $J_{3,6}$ = 0.9 Hz, py-H3), 8.87 (ddd, 1 H, $J_{6,5}$ = 4.8, $J_{6,4}$ = 1.7, $J_{6,3}$ = 0.9 Hz, py-H6).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 107.0, 118.3, 124.1, 124.8, 125.8, 125.9, 128.0, 128.6, 131.7 (quart C), 132.3 (quart C), 137.0, 141.7 (quart C), 146.0 (quart C), 149.9 (quart C), 150.4, 163.4 (quart C).

MS (EI, 70 eV): *m/z* (%) = 246 (100, M^+).

Anal. calcd for $C_{16}H_{10}N_2O$ (246.3): C 78.03, H 4.09, N 11.38; found: C 77.84, H 4.24, N 11.31.

4-Bromo-2-(2-pyridyl)naphtho[2,3-*d*]-1,3-oxazole (15)

To a solution of **14** (1.00 g, 4.06 mmol) in CH_2Cl_2 (50 mL) was added solid Na_2CO_3 (0.43 g, 4.06 mol) and a small amount of anhyd $FeCl_3$. The suspension was cooled to 0 °C and stirred vigorously while slowly adding a solution of Br_2 (650 mg, 4.06 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 15 min. Then an additional amount of Br_2 (650 mg) in CH_2Cl_2 (10 mL) was added. The mixture was allowed to warm to r.t. and stirred for 16 h. After washing with satd $NaHCO_3$ solution (2 × 30 mL) the organic phase was dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel with CH_2Cl_2/acetone (100:1). Recrystallization from CH_2Cl_2/pentane resulted in the formation of colourless crystals; yield: 0.95 g (72%); mp 225–226 °C; R_f (silica gel, CH_2Cl_2/acetone, 100:1) 0.21.

IR (KBr): ν = 3050 (C–H arom), 1640, 1610 (C=N), 1585, 1550, 1500 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 250 MHz): δ = 7.51 (ddd, 1 H, $J_{5,4}$ = 7.7, $J_{5,6}$ = 4.8, $J_{5,3}$ = 1.2 Hz, py-H5), 7.56–7.64 (m, 2 H), 7.90–8.00 (m, 3 H), 8.01 (s, 1 H, H9), 8.39–8.44 (m, 1 H), 8.56 (ddd, 1 H, $J_{3,4}$ = 7.9, $J_{3,5}$ = 1.2, $J_{3,6}$ = 0.9 Hz, py-H3), 8.87 (ddd, 1 H, $J_{6,5}$ = 4.8, $J_{6,4}$ = 1.8, $J_{6,3}$ = 0.9 Hz, py-H6).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 106.8, 112.1 (quart C), 124.7, 126.2, 126.3, 126.4, 127.0, 128.5, 130.1 (quart C), 132.9 (quart C), 137.1, 141.5 (quart C), 145.6 (quart C), 149.0 (quart C), 150.4, 163.7 (quart C).

MS (EI, 70 eV): *m/z* (%) = 324 (100, M^+) ref. to ^{79}Br.

Anal. calcd for $C_{16}H_9BrN_2O$ (325.2): C 59.10, H 2.79, N 8.62; found: C 58.88, H 2.92, N 8.43.

rac-4-(2-Methoxy-1-naphthyl)-2-(2-pyridyl)naphtho[2,3-*d*]-1,3-oxazole (16)

Under nitrogen protection compound **15** (341 mg, 1.05 mmol) and $(Ph_3P)_4Pd$ (38.6 mg, 0.033 mmol) were dissolved in ethylene glycol dimethyl ether (15 mL). A solution of **3** (211 mg, 1.05 mmol), in EtOH (1 mL), and a 2 M Na_2CO_3 solution (1.13 mL, 2.26 mmol) were added and the mixture was refluxed for 16 h. The mixture was filtered and the solid residue was washed with CH_2Cl_2 (120 mL). The combined organic phases were washed with brine (3 × 40 mL) and dried (Na_2SO_4). The solvent was removed and the residue was chromato-

graphed on silica gel with CH_2Cl_2/acetone (100:1); yield: 307 mg (73%); mp 237°C; R_f (silica gel, CH_2Cl_2/acetone, 100:1) 0.30.

IR (KBr): ν = 3070, 3010 (C–H arom), 2980, 2950, 2850 (C–H aliph), 1630 (C=N), 1600, 1560, 1510 cm^{-1} (C=C).

^1H NMR (DMSO-d_6, 400 MHz): δ = 3.74 (s, 3 H, OCH_3), 6.87 (d, 1 H, J = 8.4 Hz), 7.21 (ddd, 1 H, J = 8.4, 6.9, 1.2 Hz), 7.31–7.38 (m, 3 H), 7.56 (ddd, 1 H, J = 8.2, 5.9, 2.0 Hz), 7.61 (ddd, 1 H, $J_{5,4}$ = 7.6, $J_{5,6}$ = 4.7, $J_{5,3}$ = 1.1 Hz, py-H5), 7.73 (d, 1 H, J = 9.2 Hz, naphth-H3), 7.96 (ddd, 1 H, $J_{4,3} \approx J_{4,5}$ = 7.8, $J_{4,6}$ = 1.7 Hz, py-H4), 8.03 (d, 1 H, J = 8.1 Hz), 8.19–8.24 (m, 3 H), 8.46 (1 H, s, oxnaphth-H4), 8.78 (ddd, 1 H, $J_{6,5}$ = 4.7, $J_{6,4}$ = 1.6, $J_{6,3}$ = 0.9 Hz, py-H6).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 61.2 (OCH_3), 111.6, 119.0, 122.2 (quart C), 128.4, 129.2, 129.5, 130.0, 130.2 (quart C), 130.6, 130.7, 131.5, 131.7, 133.0, 133.4, 133.5 (quart C), 135.2 (quart C), 135.2, 137.0 (quart C), 138.3 (quart C), 142.5, 145.7 (quart C), 149.8 (quart C), 153.7 (quart C), 155.2, 159.9 (quart C), 167.9 (quart C).

MS (EI, 70 eV): *m/z* (%) = 402 (100, M^+).

Anal. calcd for $C_{27}H_{18}N_2O_2$ (402.5): C 80.58, H 4.51, N 6.96; found: C 80.31, H 4.32, N 6.80.

rac-3-Hydroxy-2'-methoxy-2-(2-pyridylcarbonyl)amino-1,1'-binaphthyl (17)

A suspension of *rac*-**16** (250 mg, 0.62 mmol) in 2 M KOH solution in MeOH (25 mL) was refluxed for 90 min during which time, the starting material had dissolved and a cloudy, yellow solution had formed. The solution was brought to pH 6–7 with concd HCl. The solution was filtered and the solvent removed. The residue was chromatographed on silica gel with CH_2Cl_2/acetone 100:1. Evaporation of the solvent gave a colourless, microcrystalline powder; yield: 209 mg (80%); mp 189°C; R_f (silica gel, CH_2Cl_2/acetone, 100:1) 0.29.

IR (KBr): ν = 3400–3600 (O–H), 3280 (N–H), 3060 (C–H arom), 2960, 2930, 2860 (C–H aliph), 1665 (C=O), 1625 (C=N), 1600, 1540, 1510 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.77 (s, 3 H, OCH_3), 7.03–7.11 (m, 3 H), 7.19 (ddd, 1 H, J = 8.4, 6.9, 1.3 Hz), 7.26–7.32 (m, 2 H), 7.36 (ddd, 1 H, J = 8.2, 5.9, 2.1 Hz), 7.50 (d, 1 H, J = 9.1 Hz), 7.61 (s, 1 H, isoquin-H4), 7.74 (ddd, 1 H, $J \approx J'$ = 7.7, J = 1.7 Hz), 7.80 (d, 1 H, J = 8.3 Hz), 7.87 (d, 1 H, J = 8.1 Hz), 8.06–8.12 (m, 3 H), 10.30 (s, 1 H, OH), 10.38 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 56.4 (OCH_3), 113.3, 114.8, 117.1 (quart C), 122.4, 123.9, 124.0, 125.0, 125.7, 126.1, 126.2 (quart C), 126.5, 126.5 (quart C), 126.7, 127.2, 128.0, 128.0 (quart C), 129.3 (quart C), 130.8, 133.3 (quart C), 133.7 (quart C), 137.5, 147.8, 148.1 (quart C), 148.6 (quart C), 154.9 (quart C), 163.6 (quart C).

MS (EI, 70 eV): *m/z* (%) = 420 (100, M^+).

Anal. calcd for $C_{27}H_{20}N_2O_3$ (420.5): C 77.13, H 4.79, N 6.66; found: C 76.95, H 4.66, N 6.48.

Optical Resolution of 7

A slow stream of HCl was passed through a cooled solution of *rac*-**7** (2.00 g, 5.52 mmol) in CH_2Cl_2 (25 mL) for 1 min resulting in an orange colour of the solution. The solvent was evaporated, and the residue and the ammonium salt of (–)-3-bromocamphor-8-sulfonic acid (1.81 g, 5.52 mmol) were dissolved in MeOH. The solution was filtered and the solvent was slowly evaporated in an open vessel leading to a mixture of two solids. One was pale yellow and crystalline, the other dark yellow and amorphous. MeOH was added until the dark yellow fraction had completely dissolved and only the pale yellow crystalline fraction was left. The solvent of the solution was evaporated and the above procedure was repeated with the residue for one or two more times until no more crystalline product formed. The combined pale yellow crystal fractions were dissolved in MeOH and the solution was passed through a strongly basic ion exchange resin to liberate the free base using additional MeOH for elution. The solvent was removed and the residue was recrystallized from CH_2Cl_2/petroleum ether (1:1) at –25°C. The crystals were filtered and discarded. The solvent from the mother liquor was evaporated and after another recrystallization step with the residue, (+)-**7** was obtained in >96%ee (see text) from the mother liquor in an overall yield of 40%, relative to the total amount of (+)-enantiomer. Through crystallization in CH_2Cl_2/petroleum ether at –25°C single crystals could be obtained. Optical rotation: $[\alpha]^{20}$ (*c* = 0.52 g/100 mL, CH_2Cl_2) +308 (589 nm), +324 (578 nm), +381 (546 nm), + 793 (436 nm).

X-ray Crystal Structure Analysis of 7

$C_{25}H_{18}N_2O \bullet CH_2Cl_2$ (447.4); crystal dimensions 0.20 × 0.95 × 0.99 mm^3; crystal system rhombic; space group D_2^4, $P2_12_12_1$, (19); unit cell dimensions: a = 9.181(3), b = 7.812(3), c = 31.19(1) Å, α = β = γ = 90°, V = 2237 $Å^3$, Z = 4; $density_{calc}$ = 1.33 g/cm^3, μ(Mo-K_α) = 0.31, 2 Θ range: 3°<2Θ<57.5°; total number of reflections 6551, unique reflections 5811, number of independent reflections with I>2.5σ 2982; F(000) = 928; R = 0.069, R_w = 0.059; diffractometer Syntex R3. The structure was solved by direct methods using the SHELXTL PLUS version 4.2/800 program system. Crystallographic data have been deposited. Further details of the crystal structure determination are available on request from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany, on quoting the depositary number CSD-408391.

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