Synthesis and Preliminary Use of Naphthyl Quinazoline and Isoquinoline Oxazolines for Asymmetric Allylic Oxidation

Merritt B. Andrus* and B. B. V. Soma Sekhar

Brigham Young University, Department of Chemistry and Biochemistry,
C100 BNSN, Provo, UT 84602-5700, USA

Received July 11, 2001

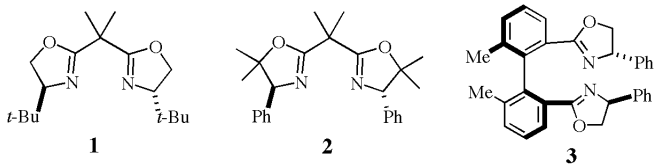
This paper is dedicated to Professor Jerald S. Bradshaw, undergraduate mentor of MBA, with warmth and gratitude for his encouragement and outstanding leadership.

Four new oxazoline ligands, 4-naphthyl-2-phenylquinazoline **4** and 1-naphthylisoquinoline **5** were made using Suzuki coupling, a Pictet-Gams reaction, and *S*-amino alcohol. Preliminary use as ligands for asymmetric copper catalyzed allylic oxidation with cyclohexene and perester showed promise providing *S*-cyclohexenyl benzoate product in moderate enantioselectivity (64%ee).

J. Heterocyclic Chem., **38**, 1265 (2001).

Bisoxazoline and oxazoline ligands derived from non-racemic amino alcohols continue to play an important role as ligands for asymmetric processes. Metal complexes with oxazoline ligands serve as catalysts for a variety of asymmetric transformations including cyclopropanation [1], aziridination [2], allylic displacement [3], imine additions [4], Diels-Alder [5] ,aldol [6],1,3-dipolar cycloaddition [7],reduction [8],and the ene reaction [9]. We and Pfaltz independently reported [10] that malonyl-derived bisoxazoline copper complexes of **1** and **2** (Scheme 1) give high selectivities (80%ee) in the Kharasch copper catalyzed allylic oxidation reaction [11], a significant improvement over earlier approaches [12]. As the utility of this class of ligands expands, efforts to improve reactivity and selectivity will depend on the availability of synthetic routes to modified bisoxazolines. While the majority of bisoxazoline ligands remain methylene and pyridyl linked, recently biaryl bisoxazoline ligands have been reported and used as ligands in asymmetric reactions [13]. We synthesized and used the *S,S,S* –bis-toluyl bisoxazoline **3** as ligand for allylic oxidations and obtained products in the 70%ee range [14].

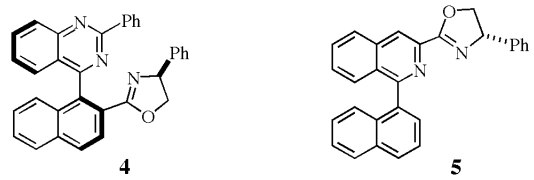
Scheme 1



1 **2** **3**

In an effort to improve reactivity and selectivity, we now report the synthesis and preliminary use of two new novel ligands, 4-naphthyl-2-phenylquinazoline **4** and 1-naphthylisoquinoline **5** (Scheme 2). Brown and others have recently produced and investigated biaryl isoquinoline-phosphines and indoles [15]. Quinazoline-phosphines have also been reported [16]. While oxazolines have been combined in ligands with sulfide and phosphine moieties, [17] oxazoline-quinazoline and isoquinoline dual-domain ligands have not been reported. The new oxazoline-quinazoline **4** was made using a Suzuki coupling and is obtained in conformationally stable *S* form. The biaryl oxazoline-isoquinoline **5**, made using a Pictet-Gams reaction, is not conformationally stable. Both were tested for use as ligands for asymmetric allylic oxidation.

Scheme 2

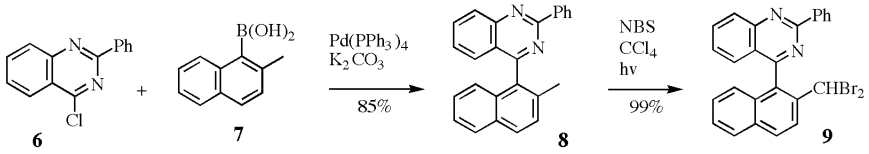


4 **5**

The synthesis of **4** began with the Suzuki coupling [18] of commercially available 4-chloro-2-phenylquinazoline **6** (AM-ex-OL) with 2-methyl-1-naphthylboronic acid [19] **7** under palladium catalysis to give the biaryl adduct **8** in 85% isolated yield (Scheme 3). Functionalization of the methyl group appended at the 2-position of the naphthyl moiety was performed using benzylic bromination. The dibromide **9** was formed using two equivalents of *N*-bromosuccinide under photolytic conditions in quantitative yield [20].

The dibromide **9** was converted to the 2-naphthaldehyde **10** silver nitrate in 70% yield following the protocol of Walsh (Scheme 4) [20]. While many options are available at this point to effect the conversion to the carboxylic acid, only treatment with potassium permanganate in an acetone-water mixture resulted in formation of **11**. Problems obtained with other reagents, *N*-oxide formation and ring cleavage were not seen in this case. The final steps follow well established routes to oxazolines form carboxylic acids and amino alcohols. Treatment with thionyl chloride provided the intermediate acid chloride, which was taken on

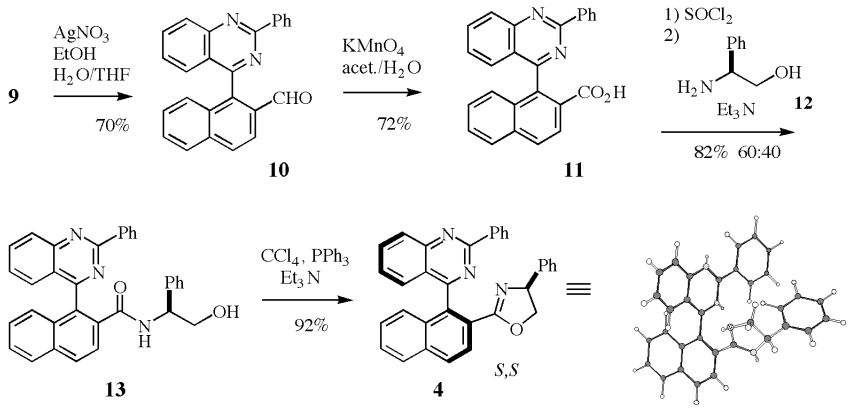
Scheme 3



in crude form to the amide. *S*-Phenylglycinol was added in the presence of triethylamine to provide product in 82% yield. As seen previously with the bitoluyl bisoxazolines **3**, the diastereomeric atropisomers **13** formed were separable at this stage by simple silica gel chromatography. The 60:40 mixture was cleanly separated at this point and the major isomer was taken on to the final reaction. Previous quinazoline-phosphines have also been resolvable, but have required enantiopure palladium co-ligand complexes [16]. The major amide **13** was converted to naphthyloxazolinyl quinazoline **4** using carbon tetrachloride and triphenylphosphine in high yield. A single crystal x-ray structure was solved for **4** and it was shown conclusively that it possessed the *S,S* configuration shown. The crystal shows the oxazoline oxygen pointing in toward the quinazoline instead of the more basic nitrogen. Upon metal exposure, this nitrogen should swing around pointing toward quinazoline N-2 to form a seven-ring chelate.

Preliminary asymmetric allylic oxidation reactions were then performed using **4** and **5** as ligands for copper complexes using cyclohexene as substrate to give ester products. Two methods were used. One with copper(I) hexafluorophosphate in acetonitrile follows previous efforts with *t*-butyl *p*-nitroperbenzoate as oxidant and the other the protocol of Singh with copper(II) triflate and phenylhydrazine with *t*-butyl perbenzoate (Table 1). In both cases only low yields were obtained. With ligand **4** the reactivity was very low, 7% with 32%ee, as

Scheme 4



The synthesis of oxazolinylisoquinoline **5** began with the treatment of racemic norephedrine **14** with 1-naphthoyl chloride **15** to give amide **16** (Scheme 5). The Pictet-Gams reaction, direct isoquinoline formation from a β-hydroxy-β-phenethylamide, was effected by treatment with P_2O_5 to give isoquinoline **17** in 62% isolated yield [21]. Benzylic monobromination was performed with NBS under photolysis conditions to provide **18**. Dibromide formation leading to an intermediate aldehyde proved problematic from **17**. Once monobromide **18** was secure, the direct aldehyde formation conditions of Ganem and Boeckman using silver tetrafluoroborate in DMS were used with success in 77% yield [22]. This material was then converted to carboxylic acid **19** in 97% yield using the previous silver nitrate reagent in the presence of base. Amide coupling with PyBrop and the amino alcohols shown gave amides **20** in good yield [23]. Oxazoline formation occurred again using carbon tetrachloride and phosphine giving the target ligands **5**. Both compounds were found to exist as rapidly interconverting atropisomers, which were not separable.

seen previously with some *S,R,S* –**3** ligands (*t*-Bu in place of Ph). With *S,S,S*- **3** the yield was 78% with 73%ee. In contrast *S,R,S* –**3** (Ph) gave ester in 76% yield and 0%ee. Ligand **5** (R=Ph) gave only slightly improved results at 44% ee. Use of phenylhydrazine, a reducing additive, gave much faster reaction times in this case with improved selectivity, 64%ee. Previously, these conditions failed to improve the reactivity of ligand **3**. Other ligands, where R=*t*-Bu, Bn, and *i*-Pr, together with other olefin substrates and various conditions can now be performed in an effort to improve reactivity and selectivity. The routes to these novel ligands should also find application to other asymmetric transformations involving metal complexes.

Scheme 5

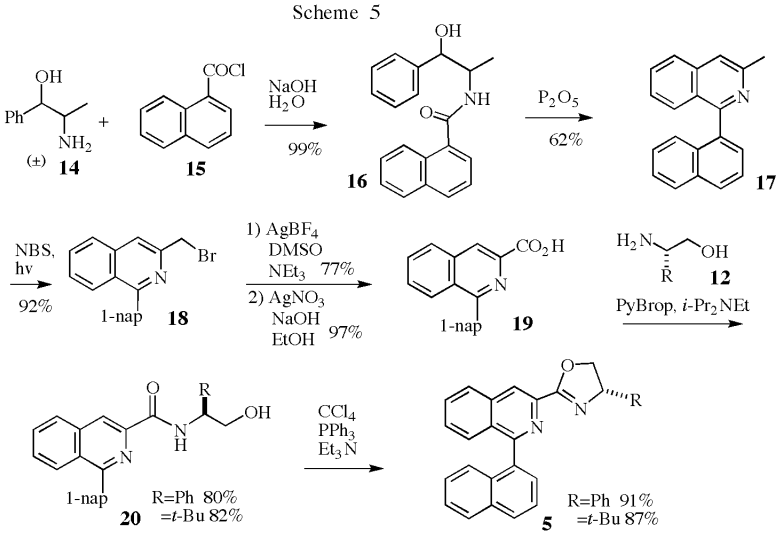
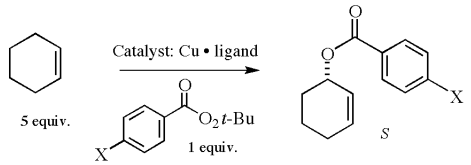


Table 1

Copper catalyzed asymmetric allylic oxidation



entry	Cu	mol%	ligand	X	solvent	°C	additive	time	yield [a]	ee [b]
1	$CuPF_6$	15	**4**	$-NO_2$	CH_3CN	-20°	-	6 d	7%	32%
2	$CuPF_6$	15	**5**	$-NO_2$	CH_3CN	-20°	-	6 d	12%	44%
3	$Cu(OTf)_2$	10	**5**	-H	acetone	rt	$PhNHNH_2$	6 h	37%	64%

[a] Yields are for chromatographed (silica gel, radial chromatotron), isolated materials (>95% ^1H and ^{13}C NMR). [b] Enantiomeric excess was determined by chiral HPLC(Chiralpak AD colunm, 0.5% *i*-PrOH/heptanes, 0.75 mL/min, 19.1 min (minor R), 21.7 min (major S)) with comparison to racemic materials.

Acknowledgment.

We are grateful for the support provided by the National Science Foundation (Career Award, CHE-9501867), Brigham Young University. We also thank Prof. N. Kent Dalley for X-ray crystallography and Mr. Bruce Jackson for mass spectroscopy.

EXPERIMENTAL

Air-sensitive reactions were performed under nitrogen. Air and moisture-sensitive reagents were introduced by syringe or cannula through rubber septa. All reaction solvents were of HPLC grade quality or distilled prior to use from an appropriate drying agent. Methylene chloride and acetonitrile were distilled from CaH_2. DMSO was dried over 4 Å molecular sieves prior to use. THF and diethyl ether were distilled from sodium benzophenone ketyl. Starting materials and reagents were purchased from Aldrich, Sigma and used without further purification. Purification by flash chromatography was carried out in the indicated solvent system using 70-230 mesh silica gel. Purification by radial chromatography was performed using 1, 2, and 4 mm plates loaded with 230-400 mesh PF-254 gypsum-bound silica. TLC analysis was conducted on silica gel 60 F_{254}, 0.25 mm precoated glass plates. All ^1H NMR spectra were obtained using either a 300 or 500 MHz spectrometer employing chloroform (7.26 ppm) or TMS (0.0 ppm) as an internal reference. Signals are reported as: m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), bd (broad doublet), bt (broad triplet), ABq (AB quartet); coupling constants (*J*) are reported in hertz (Hz). Carbon spectra were obtained at 75 or 125 MHz and referenced against deuterated $CDCl_3$. Infrared spectra were obtained using a Varian FTIR spectrometer. Mass spectra were run by the Brigham Young mass spectrometry facility. Generally, FAB or CI analysis was performed. Optical rotations were obtained using a polarimeter at rt employing the sodium D line.

Preparation of 4-(2-Methyl-naphthalen-1-yl)-2-phenyl-quinazoline (**8**).

AM-ex-OL® **6** (4.25 g, 17.65 mmol) was added as a solid to a solution of $Pd(PPh_3)_4$ (1.02 g, 0.88 mmol) in DME (100 mL) and stirred (10 minutes) under nitrogen atmosphere to give a pale yellow solution. 2-Methyl-1-naphthylboronic acid **7** (3.94 g, 21.2 mmol) was transferred as a solid. This homogenized reaction mixture turned to reddish brown by precipitation upon the addition of aqueous K_2CO_3 (2.0 *M*, 21 mL) which was subsequently refluxed overnight. The reaction mixture was cooled, filtered and concentrated. The red viscous concentrate was dissolved in CH_2Cl_2 (500 mL),and washed with brine (2 X100 mL). Usual workup and purification by silica gel chromatography furnished **8** as a fine crystalline solid (5.22 g, 85%). R_f = 0.52 (10% EtOAc/Hexanes). mp 148-150 °C. ^1H (300 MHz, $CDCl_3$): δ 8.74 -8.67 (m, 2H), 8.24 (dt, 1H, J = 0.9 and 8.5 Hz), 7.99-7.84 (m 3H), 7.57-7.50 (m, 4H), 7.39 (dd, 2H, J = 0.9 and 6.8 Hz), 7.32-7.26 (m, 1H), 7.16 (d, 1H, J = 8.0 Hz), 2.21 (s, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 169.74, 161.14, 151.46, 138.47, 134.26, 134.19, 133.12, 132.34, 132.11, 130.75, 129.31, 129.18, 129.03, 128.87, 128.76, 128.21, 127.48, 126.94, 126.75, 125.56, 125.43, 123.77, 20.43. MS (EI) *m/z* (relative Intensity): 345 (M^+ - H, 100), 266 (5), 241 (5), 173 (8), 84 (10). HRMS (EI) calcd for $C_{25}H_{18}N_2$ (M^+) 346.1470, found 346.1460.

Anal. Calcd for $C_{25}H_{18}N_2$: C, 86.68; H, 5.24; N, 8.09. Found: C, 86.73; H, 5.33; N, 7.89.

Preparation of 4-(2-Dibromomethyl-naphthalen-1-yl)-2-phenyl-quinazoline (**9**).

A mixture of **8** (1.23 g, 3.56 mmol), NBS (1.33 g, 7.47 mmol) and dibenzoyl peroxide (0.086 g, 0.35 mmol) in CCl_4 (125 mL) was heated at reflux while being irradiated by flood lamp for 6 hours. The reaction mixture was cooled, filtered and washed with benzene (100 mL). The filtrate was washed successively with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). Organic layer was dried over anhydrous $CaCl_2$, concentrated and dried under vacuum to provide the pale yellow solid **9** in quantitative yield which was used without further purification. R_f = 0.46 (10% EtOAc/hexanes). ^{1}H (300 MHz, $CDCl_3$): δ 8.73 -8.70 (m, 2H), 8.26 (d, 2H, J = 8.8 Hz), 8.17 (d, 1H, J = 8.8 Hz), 7.94 (m, 2H), 7.56-7.51 (m, 4H), 7.45 (m, 3H), 7.07 (d, 1H, J = 8.2 Hz), 6.44 (s, 1H). ^{13}C (75 MHz, $CDCl_3$): δ 166.59, 161.05, 151.53, 137.91, 137.42, 134.87, 134.50, 133.70, 134.87, 134.50, 133.70, 131.10, 130.99, 130.77, 129.42, 129.12, 128.88, 128.44, 127.90, 127.79, 127.72, 126.97, 126.94, 126.49, 123.66, 38.90.

Preparation of 1-(2-Phenyl-qunizolin-4-yl)-naphthalene-2-carbaldehyde (**10**).

To the solution of **9** (0.5 g, 0.99 mmol) in EtOH (5 mL) and THF (3 mL) at reflux was treated with aqueous $AgNO_3$ (0.5 g in 1.4 mL of H_2O, 2.94 mmol) in dropwise addition. The reaction mixture formed pale yellow precipitation. Upon reflux for a period of 1 hour it turned to grayish yellow precipitate. The mixture was filtered through a fritted disk funnel while hot and the filter cake was washed with hot THF. The combined filtrates were concentrated and subjected to gradient silica gel chromatography to provide the aldehyde **10** as a fine crystalline solid (0.25 g, 70%). R_f = 0.53 (20% EtOAc/Hexanes). mp 179-180 °C. ^{1}H (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.69 -8.65 (m, 2H), 8.28-8.14 (m, 3H), 8.03 (d, 1H, J = 8.3 Hz), 7.93 (ddd, 1H, J = 1.5, 6.8 and 8.3 Hz), 7.65 (ddd, 1H, J = 1.5, 6.8 and 8.3 Hz), 7.55-7.50 (m, 3H), 7.45 -7.34 (m, 4 H). ^{13}C (75 MHz, $CDCl_3$): δ 190.88, 166.38, 160.68, 151.20, 140.67, 137.90, 136.31, 134.70, 132.17, 131.84, 131.07, 130.26, 129.50, 129.39, 129.03, 128.85, 128.70, 128.03, 127.84, 127.27, 126.65, 124.71, 122.78. MS (EI) *m/z* (relative Intensity): 360 (M^+ + H, 60), 331 (100), 253 (13), 227(12), 165 (10), 77 (5). HRMS (EI) calcd for $C_{25}H_{16}N_2O$ (M^+) 360.1263, found 360.1263.

Anal. Calcd for $C_{25}H_{16}N_2O$: C, 83.31; H, 4.47; N, 7.77. Found: C, 82.98; H, 4.53; N, 7.92.

Preparation of 1-(2-Phenyl-qunizolin-4-yl)-naphthalene-2-carboxylic Acid (**11**).

Aldehyde (**10**), (0.31 g, 0.86 mmol) in acetone (15 mL) was heated to 60 °C and aqueous $KMnO_4$ (0.237 g in 6 mL water, 1.5 mmol) was added for 15 minutes followed by refluxing the reaction mixture for 1 hour. The reaction mixture was cooled and filtered through celite. The celite pad was washed with hot acetone. Reaction mixture was concentrated and dissolved in 75 mL of ether and neutralized with 1 *N* HCl (3 mL). Organic layer was separated , dried over anhydrous Na_2SO_4 and concentrated. The concentrate was purified by silica gel chromatography to furnished acid **11** as a fine white powder (0.227 g ,70%). R_f = 0.59 (EtOAc). mp 249-250 °C. ^{1}H (500 MHz, $CDCl_3$): δ 13.7 (br s, 1H, D_2O) exchangeable), 8.57-8.56 (m, 2H), 8.15 (d, 2 H, J = 8.7 Hz), 8.06 (d, 1H, J = 8.7 Hz), 7.97 (d, 1H, J = 8.3 Hz), 7.79 (t, 1H, J = 8.3 Hz), 7.58 (t, 1H, J = 8.3 Hz), 7.47-7.46 (m, 3H), 7.34-7.18 (m, 4H). ^{13}C (125 MHz, $CDCl_3$): δ 170.26, 160.62, 150.56, 138.70, 138.30, 135.78, 133.94, 131.94, 130.67, 129.68, 129.07, 128.96, 128.73, 128.70, 128.34, 127.58, 127.53, 127.37, 126.47, 126.33, 126.28, 124.05. MS (EI) *m/z* (relative Intensity): 360 (M^+ + H, 60), 331 (100), 253 (13), 227(12), 165 (10), 77 (5). HRMS (EI) calcd for $C_{25}H_{16}N_2O$ (M^+) 360.1263, found 360.1263.

Anal. Calcd for $C_{25}H_{16}N_2O$: C, 83.31; H, 4.47; N, 7.77. Found: C, 82.98; H, 4.53; N, 7.92.

Preparation of Amide **13**.

Acid **11** (0.10 g, 0.26 mmol) was refluxed in $SOCl_2$ (0.37 g, 0.23 mL, 3.15 mmol) for 3 hours. Reaction mixture was cooled and excess $SOCl_2$ removed under reduced pressure. The resultant glue was dried under high vacuum for 3 hours. The yellow solid acyl chloride was dissolved in dry CH_2Cl_2 at -78 °C, and transferred *via* cannula to a stirring mixture of 2(*S*)-2-phenylglycinol **12** (0.043 g, 0.31 mmol) and NEt_3 (0.145 g, 0.20 mL, 1.43 mmol) at -78 °C in CH_2Cl_2. Reaction mixture was stirred at -78 °C for 3 hours and allowed to warm slowly to room temperature overnight. Reaction mixture was concentrated under reduced pressure and dissolved in ethyl acetate (50 mL) and aqueous $NaHCO_3$ (5 mL). Usual workup and purification by radial chromatography provided separable **13**-(*Sp, S*) (0.065 g, 49%)(R_f = 0.54, 70% EtOAc/hexanes) and **13**-(*Rp, S*) (0.043 g, 32%) (R_f = 0.40, 70% EtOAc/Hexanes) diastereomeric atropisomers as white solid products. (*Sp, S*)-1-(2-Phenylquninazolin-4-yl)-naphthalene-2-carbox-[2(*S*)-2-hydroxy-1-pheynylethyl]amide (**13**): ^{1}H (300 MHz, $CDCl_3$): 8.68-6.86 (aromatic hydrogens, 20H), 6.64 (d, 1H, amide NH, J = 5.8 Hz), 4.66 (dd, 1H, J = 5.8 and 5.6 Hz), 3.20 (m, 2 H). ^{13}C (125 MHz, $CDCl_3$): δ 168.97 (NHC=O), aromatic signals, 66.08, 56.49. MS (EI) *m/z* (relative Intensity): 495 (M^+, 3), 358 (100). HRMS (EI) calcd for $C_{33}H_{25}N_3O_2$(M^+) 495.1947, found 495.1956. (*Rp, S*)-1-(2-phenylquninazolin-4-yl)-naphthalene-2-carbox-[2(*S*)-2-hydroxy-1-pheynylethyl]-amide (**13**): ^{1}H (500 MHz, $CDCl_3$): 8.57-6.48 (aromatic H, 20H), 6.72 (d, 1 H, amide NH, J =5.6 Hz), 4.72 (dd, 1H, J = 5.6 and 5.6 Hz), 3.56 (t, 2H, J = 5.6 Hz). ^{13}C (125 MHz, $CDCl_3$): δ 168.98 (NHC=O), aromatic signals, 66.41, 56.68.

Procedure for the Synthesis of Oxazoline-quinazoline (**4**).

A solution of amide **13** (1 equivalent), PPh_3 (1.2 equivalent), NEt_3 (1.75 equivalent), and CCl_4 (3.4 equivalent), in dry acetonitrile were refluxed for 6 hours. After being cooled, the brown reaction mixture was concentrated under reduced pressure. The residue was extracted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine. Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The concentrate was subjected to purification by radial chromatography to furnish the desired oxazolines. (*Sp, S*) Oxazoline-**4**: (*S*)-2-Phenyl-4-[(*S*)-2-(4(*S*)-phenyl-4,5-dihydro-oxazol-2-yl)-naphthalen-1-yl]quinazoline**:** R_f = 0.50 (25% EtOAc/hexanes). mp 190 °C. $[\alpha]_D$ -168 (c = 1.1, $CHCl_3$). ^{1}H (500 MHz, $CDCl_3$): δ 8.70-7.76 (m, 2H), 8.28 (d, 1H, J = 8.8 Hz), 8.20 (d, 1H, J = 8.3 Hz), 8.12 (d, 1H, J =8.3 Hz), 8.01 (d, 1H, J = 8.3 Hz), 7.90(ddd, 1H, J = 1.4, 7.5, and 7.5 Hz), 7.60-7.57 (m, 1H), 7.53-7.45 (m, 4H), 7.42-7.36 (m, 3H), 7.16-7.08 (m, 3H), 6.86-8.64 (m, 2H), 5.07 (dd, 1H, J = 8.3 and 10.2 Hz), 4.17 (dd, 1H, J = 8.3 and 10.2 Hz), 3.71 (t, 1H, J = 8.3Hz). ^{13}C (125 MHz, $CDCl_3$): δ 169.34, 164.72, 160.65, 150.99, 142.08, 138.44, 135.80, 134.90,

133.78, 132.03, 130.71, 129.61, 129.21, 129.08, 128.75, 128.68, 128.43, 127.80, 127.47, 127.44, 127.28, 127.12, 126.71, 126.59, 126.41, 125.35, 124.40, 74.98, 70.11. MS (EI) *m/z* (relative Intensity): 477 (M^+, 60), 447 (35), 359 (45), 246 (25). HRMS (EI) calcd for $C_{33}H_{23}N_3O$ (M^+) 477.1841, found 477.1854. (*Rp, S*) Oxazoline-**4**: (*R*)-2-Phenyl-4-[-2-(4(*S*)-phenyl-4,5-dihydro-oxazol-2-yl)-naphthalen-1-yl]quinazoline**:** R_f = 0.40 (25% EtOAc/hexanes). mp 182 °C. $[\alpha]_D$ + 8.2 (c = 1.1, $CHCl_3$). ^1H (500 MHz, $CDCl_3$): δ 8.71-8.68 (m, 2H), 8.27 (d, 1H, J = 8.7 Hz), 8.18 (d, 1H, J = 8.3 Hz), 8.11 (d, 1H, J = 8.7 Hz), 8.00 (d, 1H, J = 8.3 Hz), 7.86 (ddd, 1H, J = 1.4, 7.8, and 7.8 Hz), 7.59-7.56 (m, 1H), 7.55-7.49 (m, 3H), 7.46 (dd, 1H, J = 0.9 and 7.8 Hz), 7.41-7.35 (m, 3H), 7.14-7.11 (m, 1H), 7.06 (t, 2H, J = 7.8 Hz), 6.87 (d, 2H, J = 7.8 Hz), 5.07 (dd, 1H, J = 8.3 and 10.2 Hz), 4.33 (dd, 1H, J = 8.3 and 10.2 Hz), 3.56 (t, 1H, J = 8.3 Hz). ^{13}C (125 MHz, $CDCl_3$): δ 169.34, 164.72, 160.65, 150.99, 142.08, 138.44, 135.80, 134.90, 133.78, 132.03, 130.71, 129.61, 129.21, 129.08, 128.75, 128.68, 128.43, 127.80, 127.47, 127.44, 127.28, 127.12, 126.71, 126.59, 126.41, 125.35, 124.40, 74.98, 70.11. MS (EI) *m/z* (relative Intensity): 477 (M^+, 100), 447 (25), 359 (55), 331 (100). HRMS (EI) calcd for $C_{33}H_{23}N_3O$ (M^+) 477.1841, found 477.1857.

Preparation of Naphthalene-1-carboxylic Acid (2-Hydoxy-1-methyl-2-phenylethyl)-amide (**16**).

A solution of 1-naphthoyl chloride **15** in (2.78 g, 2.2 mL, 14.59 mmol) in CH_2Cl_2 (20 mL) was added to a stirred mixture of norephedrine **14** (2.0 g, 13.22 mmol) in CH_2Cl_2 (100 mL) and 5% aqueous NaOH (26 mL). Reaction was allowed to stir for 6 hours after the completion of the addition. The resultant white solid formed was filtered, and the filter cake was washed with water, *i*-PrOH and ether successively followed by drying under high vacuum in a dessicator containing anhydrous P_2O_5 as a desiccant to provide **16** (3.99 g, 99%). R_f = 0.49 (50% EtOAc/Hexanes). mp 150-152 °C. ^1H (300 MHz, $CDCl_3$): δ 8.28-8.25 (m, 1H), 7.91-7.84 (m, 2H), 7.54-7.51 (m, 4H), 7.44-7.25 (m, 5H), 6.12 (d, 1H, J = 8.0 Hz), 4.98 (d, 1H, J = 2.9 Hz), 4.69-4.58 (m, 1H), 3.59 (br s, 1H), 1.16 (d, 3H, J = 7.1 Hz). ^{13}C (75 MHz, $CDCl_3$): δ 170.44, 140.79, 134.31, 133.88, 131.01, 130.27, 128.55, 128.51, 127.94, 127.44, 126.69, 126.65, 125.51, 125.21, 124.89, 51.82, 15.29. MS (CI) *m/z* (relative Intensity): 306 (M^+ + H, 80), 288 (100), 199 (15), 155 (20), 107 (15). HRMS (CI) calcd for $C_{20}H_{20}NO_2$ (M^+ + H) 306.1494, found 306.1500.

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.72; H, 6.29; N, 4.68.

Preparation of 3-Methyl-1-naphthalene-1-yl-isoquinoline (**17**).

A mixture of **16** (5.0 g, 0.016 mol) and P_2O_5 (16.3 g, 0.114 mol) was refluxed in *o*-dichlorobenzene (125 mL) at 180 °C for 24 hours. The mixture was cooled and most of the solvent was decanted. The black residual matter in the flask was washed with benzene (3 x 20 mL) and water (50 mL) was added cautiously. When the vigorous reaction stopped, it was made basic with 50% aqueous NaOH by cooling the reaction mixture. The solid material dissolves forming a dark reddish brown slurry after 2-3 hours. At this stage reaction mixture was diluted with excess ether and solid NaCl was added to breakup the suspension. The ether layer was decanted and the solid material was extracted again with ether. This process was repeated several times till there was no indication of the product in the extracted ether. All the ethereal layers were concentrated and the crude was once again washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Silica gel column chromatographic purification of the concentrate gave **8** (2.73 g, 62%) as a reddish foam which was subsequently recrystallized in 10% ethyl acetate/hexanes. mp 125 °C. R_f = 0.55 (10% EtOAc/Hexanes). ^1H (300 MHz, $CDCl_3$): δ 8.02-7.98 (m, 1H), 7.95 (d, 1H, J = 8.3Hz), 7.82 (d, 1H, J = 8.3 Hz), 7.65-7.41 (m, 7H), 7.35-7.26 (m, 2H), 2.82 (s, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 160.04, 151.10, 137.25, 133.83, 132.46, 130.24, 128.83, 128.31, 127.79, 127.70, 126.53, 126.35, 126.29, 126.18, 125.99, 125.39, 118.40, 24.62. MS (CI) *m/z* (relative Intensity): 270 (M^+ + H, 100). HRMS (CI) calcd for $C_{20}H_{16}N$ (M^+ + H) 270.1283, found 270.1264.

Preparation of 3-Bromomethyl-1-naphthalene-1-yl-isoquinoline (**18**).

A mixture of **17** (3.53 g, 13.11 mmol), NBS (2.56 g, 14.38 mmol) and dibenzoyl peroxide (0.32 g, 1.32 mmol) in CCl_4 (200 mL) was heated at reflux for 12 hours. Analogous workup as described previously provided the crude bromide **18** (4.51, 99%) as a pale red solid which was used without further purification. R_f = 0.55 (25% EtOAc/Hexanes). ^1H (300 MHz, $CDCl_3$): δ 8.05-7.91 (m 4H), 7.72-7.60 (m, 4H0, 7.53-7.33 (m, 4H), 4.88 & 4.84 (d, AB q, J = 11.1 Hz). ^{13}C (75 MHz, $CDCl_3$): δ 160.95, 149.60, 137.14, 136.54, 133.93, 132.37, 130.80, 129.22, 128.43, 127.99, 127.91, 127.87, 127.74, 127.19, 126.61, 126.19, 126.08, 125.35, 119.80, 35.11. MS (EI) *m/z* (relative Intensity): 349 (M^+ + 2, 10), 349 (M^+, 10), 302 (50), 268 (100). HRMS (EI) calcd for $C_{20}H_{14}BrN$ (M^+) 347.0310, found 347.0294.

Preparation of 1-Naphthalen-1-yl-isoquinoline-3-carbaldehyde.

Dry DMSO (22 mL) was added to the mixture of **18** (5.0 g, 14.35 mmol) and $AgBF_4$ (4.52 g, 23.21 mmol), protected from light and stirred the yellow green slurry at room temperature. NEt_3 (2.2 mL) was added to the reaction mixture and stirring was continued for an additional period of 30 minutes. The reaction mixture was diluted with ether and filtered through celite by decanting the ethereal layer. The black residue was extracted with ether by swirling and filtering through celite. The filtrate was concentrated and dried under high vacuum. The pure aldehyde (3.3 g, 77%) was obtained by subjecting the purification of the concentrate by silica gel column chromatography purification. R_f = 0.47 (25% EtOAc/hexanes). mp 170-172 °C. ^1H (300 MHz, $CDCl_3$): δ 10.35 (s, 1H), 8.53 (d, 1H, J = 1.0 Hz), 8.14 (d, 1H, J = 8.3 Hz), 8.05 (dd, 1H, J = 2.0 and 7.3 Hz), 7.98 (d, 1H, J = 7.3 Hz), 7.80 (ddd, 1H, J = 1.4, 7.1 and 8.3 Hz), 7.70-7.49 (m, 5H), 7.36-7.34 (m, 2H). ^{13}C (75 MHz, $CDCl_3$): δ 194.22, 161.62, 146.38, 136.22, 136.15, 133.92, 132.28, 131.39, 130.59, 130.25, 129.53, 129.27, 128.60, 128.26, 127.92, 126.77, 126.35, 125.85, 125.45, 120.78. MS (EI) *m/z* (relative Intensity): 283 (M^+, 70), 282 (100), 268 (40), 254 (30), 226 (8). HRMS (EI) calcd for $C_{20}H_{13}NO$ (M^+) 283.0997, found 283.0988.

Anal. Calcd for $C_{20}H_{13}NO$ C, 84.78; H, 4.62; N, 4.94. Found: C, 84.62; H, 4.73; N, 4.82.

Preparation of 1-Naphthalen-1-yl-isoquinoline-3-carboxylic Acid (**19**).

To a solution of aldehyde (0.093 g, 0.33 mmol) in absolute ethanol (2 mL) was added $AgNO_3$ (0.167 g, 0.5 mL) in water (0.5 mL). To this stirring solution, NaOH (0.04 g, 1.0 mmol) in water (0.5 mL) was added. After the addition was complete, the black

reaction slurry was filtered through celite and the filter cake was washed with Et_2O and then neutralized with 1 *M* HCl. The combined filtrates were mixed, ethereal layer separated and the aqueous layer was extracted with ether. Organic layer was dried over anhydrous Na_2SO_4 and concentrated and dried under vacuum to give **19** (0.096 g, 97%) as a pale yellow solid. ^{1}H (300 MHz, $CDCl_3$): δ 11.81 (br s, 1H), 8.75 (s, 1H), 8.22 (d, 1H, J = 8.3 Hz), 8.05 (d, 1H, J = 7.8 Hz), 7.98 (t, 1H, J = 7.3 Hz), 7.90 (d, 1H, J = 8.3 Hz), 7.72-7.59 (m, 4H), 7.44 (t, 1H, J = 7.3 Hz), 7.28 (t, 1H, J = 7.8 Hz), 7.16 (d, 1H, J = 8.3 Hz). ^{13}C (75 MHz, $CDCl_3$): δ 163.43, 159.54, 137.84, 135.82, 134.78, 133.56, 131.80, 131.68, 131.30, 130.83, 129.60, 129.51, 129.09, 128.82, 127.65, 126.86, 125.42, 125.20, 124.69. MS (CI) *m/z* (relative Intensity): 300 (M^+ + H, 100). HRMS (CI) calcd for $C_{20}H_{14}NO_2$ (M^+ + H) 300.1024, found 300.1037.

General Procedure for the Preparation of Amides **20**.

To the acid **19** (0.125 g, 0.41 mmol) in dry methylene chloride (20 mL) at 0 °C, PyBrop (0.25 g, 0.530 mmol) was added under nitrogen and stirred for 10 minutes. 2(*S*)-2-Phenylglycinol (0.067 g, 0.49 mmol) was added to this pale yellow clear solution and allowed to stir for 10 min. *i*-Pr_2NEt (0.18 g, 0.24 mL, 1.37 mmol) was added dropwise for 7 minutes. The solution turned to clear pale yellow after the addition was completed. Contents were stirred at 0 °C for 3 hours followed by stirring overnight. Reaction mixture was concentrated, diluted with EtOAc (50 mL) and water (10 mL). Organic layer was separated and the aqueous layer was back extracted with EtOAc (3 X 10 mL). The organic layers were combined, washed with 1 *N* HCl (5 mL), aqueous $NaHCO_3$ (5 mL) and brine and dried over anhydrous Na_2SO_4. Concentration followed by the purification gave **20** (0.14, 80%). R_f = 0.53 (70% EtOAc/hexanes). ^{1}H (500 MHz, $CDCl_3$): δ 8.80 & 8.74 (d, 1H, J = 7.3 Hz), 8.69 (d, 1H, J = 3.0 Hz), 8.05 (d, 1H, J = 8.3Hz), 7.99 (d, 1H, J = 7.3Hz), 7.94 (t, 1H, J = 7.3 Hz), 7.72 (t, 1H, J = 7.8 Hz), 7.65-7.45 (m, 5H), 7.40-7.21 (m, 7H), 5.32-5.26 (m, 1H), 3.86 (br s, 2H), 3.21 & 3.09 (br s, 1H). ^{13}C (125 MHz, $CDCl_3$): δ. 165.75 & 165.64, 159.56 & 159.48, 142.76, 139.21, 137.01 & 136.92, 136.61 & 136.51, 133.88 & 133.80, 132.43, 131.05, 129.68, 129.35 & 129.34, 129.05, 128.96 & 128.94, 128.74, 128.58 & 128.57, 128.16 & 128.13, 128.09 & 128.04, 127.92 & 127.89, 127.09 & 127.04, 126.71 & 126.64, 126.33 & 126.31, 126.05, 125.34 & 125.32, 120.62 & 120.52, 66.89, 56.84 & 56.56. MS (CI) *m/z* (relative Intensity): 419 (M^+ + H, 80), 401 (19), 387 (20), 299 (10). HRMS (CI) calcd for $C_{28}H_{22}N_2O_2$ (M^+ + H) 419.1760, found 419.1758. **20** (R=*t*-Bu) was also prepared from **19** in an analogous manner.

Preparation of Isoquinoline-oxazoline (**5**).

Compound **5** was prepared following the procedure as described for oxazoline **4**; **5** (R=Ph)**:** R_f = 0.58 (50% EtOAc/hexanes). $[\alpha]_D$ -27.2 (c = 3.4, $CHCl_3$). ^{1}H (500 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.00 (d, 1H, J = 8.3 Hz), 7.98 (dd, 1H, J = 1.4 and 7.8 Hz), 7.92 (d, 1H, J = 7.8 Hz), 7.70 (t, 1H, J = 7.3 Hz), 7.63-7.57 (m, 3H), 7.46 (m, 2H), 7.39-7.24 (m, 7H), 5.58 (t, 1H, J = 9.3 Hz), 4.93-4.88 (over lapped dd, 1H, J = 9.3 and 8.3 Hz), 4.89 (overlapped t, 1H, J = 8.3 Hz). ^{13}C (125 MHz, $CDCl_3$): δ. 164.82 & 164.80, 161.06 & 161.05, 142.30, 139.89 & 139.86, 136.71 & 136.67, 136.26 & 136.23, 133.73 & 133.69, 132.55, 130.97, 129.38, 129.11, 128.97, 128.91, 128.33, 128.20, 128.18, 128.06, 128.02, 127.82, 127.09, 126.44, 126.17, 126.03, 126.02, 125.43, 125.39, 122.23 75.67 & 75.66, 70.44. MS (CI) *m/z* (relative Intensity): 401 (M^+ + H, 100), 333 (15). HRMS (CI) calcd for $C_{28}H_{21}N_2O$ (M^+ + H) 401.1654, found 401.1659. **5** (R=*t*-Bu)**:** R_f = 0.64 (50% EtOAc/hexanes). $[\alpha]_D$ -84.3 (c = 2.6, $CHCl_3$). ^{1}H (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.03-7.97 (m, 2H), 7.92 (d, 1H, J = 8.3 Hz), 7.73-7.67 (m, 1H), 7.64-7.54 (m, 3H), 7.49-7.40 (m, 2H), 7.35-7.25 (m, 2H), 4.52-4.45 (overlapped dd, 1H, J = 8.8 and 10.3 Hz), 4.35 (overlapped t, 1H, J= 8.3 Hz), 4.17 (dd, 1H, J = 8.3 and 10.8 Hz). 1.03 (s, 9 H). ^{13}C (125 MHz, $CDCl_3$): δ 163.50, 160.81 & 160.78, 140.31 & 140.24, 136.85 & 136.71, 136.30 & 136.22, 133.76 & 133.66, 132.59 & 132.55, 130.82, 129.22 & 129.20, 129.06, 128.69, 128.30, 128.16, 128.07, 127.92, 126.41& 126.36, 126.22 & 126.18, 126.01 & 125.97, 125.47 & 125.33, 121.81 & 121.77, 76.46 & 76.45, 69.63, 34.24, 26.19 & 26.17. MS (EI) *m/z* (relative Intensity): 380 (M^+, 30), 323 (100), 295 (60), 279 (17), 253 (35). HRMS (EI) calcd for $C_{26}H_{24}N_2O$ (M^+ + H) 380.1889, found 380.1896.

Asymmetric Allylic Oxidation using the Ligands (**4**) and (**5**).

Degassed acetonitrile (2 mL) containing ligand (0.031 mmol) and $Cu(CH_3CN)_4PF_6$ (0.031 mmol) was stirred for 3hours. Freshly distilled cyclohexene (1.04 mmol) and *t*-butyl *p*-nitro perbenzoate (0.21 mmol) were added to the above bright yellow reaction mixture, freeze-thawed under vacuum for three cycles under nitrogen, and allowed to stir at -20 °C. The reaction progress was monitored intermittently by TLC for the disappearance of perester for 7 days. At this stage the reaction was concentrated under reduced pressure and dissolved in ether (20 mL) and aqueous ammonia (3 mL). The ether layer was further washed with aqueous ammonia until the disappearance of the blue color of the aqueous layer. Organic layer was washed with brine (3 mL), dried over anhydrous Na_2SO_4 and concentrated. The concentrate was purified by radial chromatography to obtain the 2-cyclohexenyl *p*-nitrobenzoate. See table 1 for yields and selectivities.

REFERENCES AND NOTES

[1] D. A. Evans, K. A. Woerpel, M. M. Hinman, and M. M. Faul, *J. Am. Chem. Soc.*, **113**, 726 (1991); R. E. Lowenthal and S. Masamune, *Tetrahedron Lett.*, **32**, 7373 (1991).

[2] D. A. Evans, M. M. Faul and M. T. Bilodeau, *J. Am. Chem. Soc.*, **116**, 2742 (1994); K. B. Hansen, N. S. Finney and E. N. Jacobsen, *Angew. Chem., Int. Ed. Engl.*, , **34**, 676 (1995).

[3] U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt and A. Pfaltz, *Tetrahedron*, **48**, 2143 (1992).

[4] S. E. Denmark, N. Nakajima, O. J. -C. Nicaise, A. -M. Faucher and J. P. Edwards, *J. Org. Chem.*, **60**, 4884 (1995).

[5] E. J. Corey and K. Ishihara, *Tetrahedron Lett.*, **33**, 6807 (1992); D. A. Evans, S. J. Miller and T. Lectka, *J. Am. Chem. Soc.*, **115**, 6460 (1993); D. A. Evans, J. A. Murry, P. von Matt, R. D. Norcross and S. J. Miller, *Angew. Chem., Int. Ed. Engl.*, **34**, 798 (1995).

[6] D. A. Evans, J. A. Murry and M. C. Kozlowski, *J. Am. Chem. Soc.*, **118**, 5814 (1996); D. A. Evans, M. C. Kozlowski, C. S. Burgey, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **119**, 7893 (1997).

[7] K. V. Gothelf, R. G. Hazell and K. A. Jorgensen, *J. Org. Chem.*, **63**, 5483 (1998).

[8] M. Bandini, P. G. Cozzi, L. Negro and A.Umani-Ronchi, *Chem. Commun*., 39 (1999).

[9] D. A. Evans, C. S. Burgey, N. A. Paras, T. Vojkovsky ans S. W Tregay, *J. Am. Chem. Soc.*, , **120**, 5824 (1998).

[10] M. B. Andrus, A. B. Argade, X. Chen and M. G. Pamment, *Tetrahedron Lett.*, **36**, 2945 (1995); A. S. Gokhale, A. B. E. Minidis and

A. Pfaltz, *Tetrahedron Lett.*, **36**, 1831 (1995).

[11] D. J. Rawlinson and G. Sosnovsky, *Synthesis*, 1 (1972); M. S. Kharasch, G. Sosnovsky and N. C. Yang, *J. Am. Chem. Soc.*, **81**, 5819 (1959).

[12] D. B. Denney, R. Napier and A. Cammarata, *J. Org. Chem.*, **30**, 3151 (1965); J. Muzart, *J. Mol. Catal.*, **64**, 381 (1991); A. Levina and J.Muzart, *Tetrahedron: Asymmetry*, **6**, 147 (1995).

[13] T. G. Gant, M. C. Noe and E. J. Corey, *Tetrahedron Lett.*, **36**, 8745 (1995); Y. Uozumi, H. Kyota, E. Kishi, K. Kitayama and T. Hayashi, *Tetrahedron: Asymmetrtry*, **7**, 1603 (1996); Y. Uozumi, K. Kato and T. Hayashi, *J. Am. Chem. Soc.*, **119**, 5063 (1997); Y. Imai, W. Zhang, T. Kida, Y. Nakatsuji and I. Ikeda, *Tetrahedron Lett.*, **38**, 2681 (1997); A. J. Rippert, *Helv. Chim. Acta*, **81**, 676 (1998).

[14] M. B. Andrus and D. Asgari, *Tetrahedron*, **56**, 5775 (2000); M. B. Andrus, D. Asgari and J. Sclafani, *J. Org. Chem.*, **62**, 9365 (1997).

[15] N. W. Alcock, J. B. Brown and D. I. Hulmes, *Tetrahedron: Asymmetry*, **4**, 743 (1993); H. Doucet and J. M. Brown, *Tetrahedron: Asymmetry*, **8**, 3775 (1997); T. D. W. Claridge, J. M. Long, J. M. Brown, D. Hibbs and M. B. Hursthouse, *Tetrahedron*, **53**, 4035 (1997).

[16] V. G. Chapoulaud, J. Audoux, N. Ple, A. Turck and G. Queguiner, *Tetrahedron Lett.*, **40**, 9005 (1999); P. M. Lacey, C. M. McDonnell and P. J. Guiry, *Tetrahedron Lett.*, **41**, 2475 (2000).

[17] G. J. Dawson, C. G. Frost, M. J. Williams and S. J. Coote, *Tetrahedron Lett.*, **34**, 3149 (1993); G. J. Dawson, C. G. Frost, C. J. Martin and M. J. Williams, *Tetrahedron Lett.*, **34**, 7793 (1993).

[18] N. Miyaura and A. Suzuki, *J. Chem. Soc. Chem. Commun.*, 866 (1979).

[19] S. –O. Lawesson, *Acta. Chem. Scand.*, *11*, 1075 (1957).

[20] D. A. Walsh, L. F. Sancilio and D. L. Reese, *J. Med. Chem.*, **21**, 582 (1978).

[21] W. M. Whaley and W. H. Hartung, *J. Org. Chem.*, **14**, 650 (1949).

[22] B. Ganem and R. K. Boeckman, Jr., *Tetrahedron Lett.*, **11**, 917 (1974).

[23] J. Coste, E. Ferot, P. Jouin and B. Castro, *Tetrahedron Lett.*, **32**, 1967 (1991).