JOC*Note*

Improved Synthesis of Aza-bis(oxazoline) Ligands

Heiko Werner, Robert Vicha, Anja Gissibl, and Oliver Reiser*

Institut für Organische Chemie der Universität Regensburg, Universitätsstrasse 31, D-93040 Regensburg, Germany

oliver.reiser@chemie.uni-regensburg.de

Received July 27, 2003

Abstract: A straightforward synthesis of chiral aza-bis(oxazoline) (Azabox) ligands from commercially available amino alcohols is described. The new protocol allows access to previously reported Azabox ligands in considerably improved yields but also to new derivatives, including non-C_2-symmetrical ones.

Despite the tremendous advances being made in the development of highly reactive and selective homogeneous catalysts,[1] large-scale applications will nevertheless make their efficient recovery desirable. Consequently, the immobilization of chiral catalysts onto heterogeneous supports is a logical concept to arrive at asymmetric heterogeneous catalysts. However, polymer-bound catalysts suffer in general from low reactivity and selectivity; moreover, loss of metal due to leaching from the ligand is a quite common interference. Therefore, intensive research efforts are being undertaken to design new supports and ligands to arrive at immobilized chiral catalysts[2] that will rival their nonbond counterparts in reactivity and selectivity but will also be recoverable and reusable.

Bis(oxazoline) ligands **1** have proved to be a privileged class of chiral ligands, being able to form complexes with a broad variety of metals that are able to catalyze a great number of reactions with unparalleled enantioselectivity.[3,4] Representative examples include the copper-catalyzed cyclopropanation,[4a−f,q] aziridinations,[4c,g] Diels−Alder,[4h−m] aldol reactions,[4n,o] 1,4 conjugate additions,[4p] allylic oxidations,[4x,y] ruthenium-catalyzed oxidations,[4q,r] palladium-catalyzed allylations,[4s] or rhodium-catalyzed hydrosilylations.[4t−w]

Recently, we introduced aza-bis(oxazolines)[5] **2** which can be viewed as structural hybrids of bis(oxazolines) **1** and aza-semicorrins[3,6] **3.** They combine the advantage of being accessible from the chiral pool like the bis(oxazolines) and the structural variability of aza-semicorrins due to the possibility of functionalizing the central nitrogen atom. In particular, **2** could be efficiently attached to a poly(ethylene glycol) support, which represented at this time one of the first examples of a bis(oxazoline) ligand being covalently immobilized.[7] Subsequently, there had been many more reports elegantly demonstrated different strategy to attach bis(oxazoline) ligands to polymers.[8]

(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A.,Yamamoto, H, Eds.; Springer: Berlin, 1999; Vols. 1−3. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993. (d) Kagan, H. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon: Oxford, 1992; Vol. 8. (e) *Transition Metals for Organic Synthesis*; Beller, M., Bohm, C., Eds.; Wiley-VCH: Weinheim, 1998.

(2) Reviews: (a) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217−3274. (b) Bergreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345−3384. (c) Fan, Q.-H.; Li, Y.-M.; Chan, A.-S.-C. *Chem. Rev.* **2002**, *102*, 3385−3466. (d) Song, C. E.; Li, S.-G. *Chem. Rev.* **2002**, *102*, 3495−3524. (e) van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Rev.* **2002**, *102*, 3717−3756. (f) McNamara, C. A., Dixon M. J., Bradley M. *Chem. Rev.* **2002**, *102*, 3275−3300. (g) Dickerson T. J.; Reed, N. N., K. D. Janda. *Chem. Rev.* **2002**, *102*, 3325−3344. (h) Lu, Z.-L.; Lindner E.; Mayer, H. A. *Chem. Rev.* **2002**, *102*, 3543−3578. (i) De Vos, D. E., Dams, M.; Sels, B. F.; Jacobs, P. A. *Chem. Rev.* **2002**, *102*, 3615−3640. (j) Braun, R.; Huedicke, A.; Meissner, D. *Nachrichten aus der Chemie* **2001**, *49*, 1419−1423. (k) Kobayashi, S.; Akiyama, R. *Chem. Com.* **2003**, 449−460. (l) Bianchini, C.; Barbaro, P. *Topics in Catalysis* **2002**, *19*, 17−32.

(3) Reviews: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45. (b) Jorgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (d) Pfaltz, A. *Synlett* **1999**, 835−842. (e) Pfaltz, A. *Heterocycl. Chem.* **1999**, *36*, 1437−1451. (f) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339−345. (g) Doyle, M. P.; Protopova, M. N. *Tetrahedron* **1998**, *54*, 7919−1946. (h) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, 991−1002. (i) Meyers, A. I.; Price, A. *J. Org. Chem.* **1998**, *63*, 412−413. (j) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297−2360. (k) Reiser, O. *Nachr. Chem. Technol. Lab.* **1996**, *44*, 744−750. (g) Bolm, C. *Angew. Chem.* **1991**, *103*, 556−558.

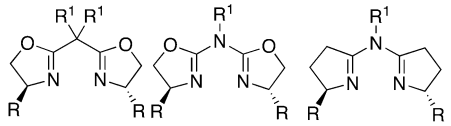
(4) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005−6008. (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373−7376. (c) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. (d) Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 4073−4076. (e) Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518−2526. (f) Boulch, R.; Scheurer, A.; Mosset, P.; Saalfrank, R. W. *Tetrahedron Lett.* **2000**, *41*, 1023−1026. (g) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328−5329. (h) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807−6810. (i) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573. (j) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7482−7594. (k) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem.* **1998**, *110*, 3554−3557. (l) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757−5762. (m) Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, *52*, 7321−7328. (n) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685. (o) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699. (p) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser O. *Org. Lett.* **2001**, *3*, 4259−4262. (q) End, N.; Pfaltz, A. *Chem. Commun.* **1998**, 589−590. (r) End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem. Eur. J.* **1998**, *4*, 818−824. (s) Müller, K.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232−240. (t) Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K, *Tetrahedron: Asymmetry* **1993**, *4*, 143−150. (u) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846−848. (v) Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 2453−2462. (w) Lee, S.; Lim, C. W.; Song, C. E.; Kim, I. O.; Jun, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2927−2932. (x) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831−1834. (y) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945−2948.

(5) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *14*, 2045−2048.

(6) (a) Fritschi, H.; Leutenegger, U.; Siegmann, K.; Pfaltz, A.; Keller, W.; Kratky, C. *Helv. Chim. Acta* **1988**, *71*, 1541−1552. (b) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553−1565. (c) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143-2156. (d) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem.* **1989**, *101*, 61−62; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 60−61.

(7) Hallmann, K.; Mecedo, E.; Nordström, K.: Moberg, C. *Tetrahedron: Asymmetry* **1999**, *10*, 4037−4046. (b) Brunner, H.; Brandl, P. *Z. Naturforsch.* **1992**, *47b*, 609−613. (c) Chow, H. F.; Mak, C. C. *J. Org. Chem.* **1997**, *62*, 5116−5127.

10.1021/jo0350920 CCC: $25.00
Published on Web 11/21/2003



1 **2** **3**

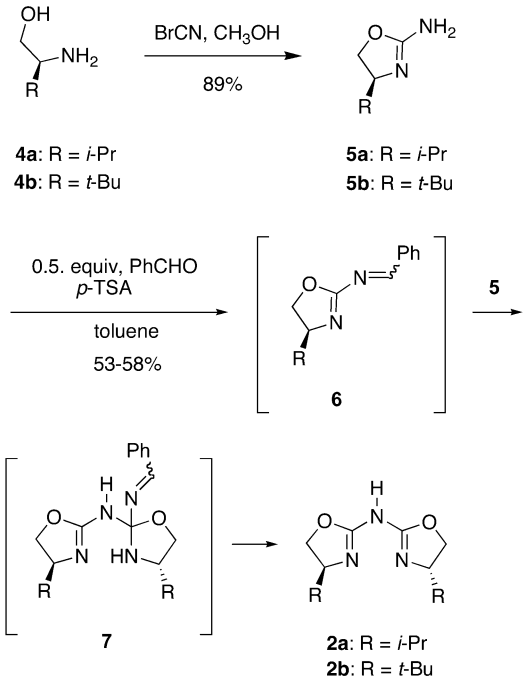
Our initial protocol for the synthesis of aza-bis(oxazolines) **2** made use of amino-oxazolines **5**, being readily available following a protocol of Poos et al.[9] In the presence of 0.5 equiv of benzaldehyde, a formal acid-catalyzed dimerization of **5** takes place, resulting in the formation of **2** in moderate yields (Scheme 1). However, purification of the ligands turned out to be problematic in many cases so that only the isopropyl and *tert*-butyl substituted aza-bis(oxazolines) **2a** and **2b** could be obtained in pure form.[5]

In attempts to improve our initial synthesis, we envisioned that a more reactive oxazoline[10] with a better leaving group than the in situ generated imines **6** might be a more suitable coupling partner. Moreover, competing nucleophilic attack on the newly generated imine carbon in **6** could also occur, which might be an explanation for some byproducts observed in this procedure.

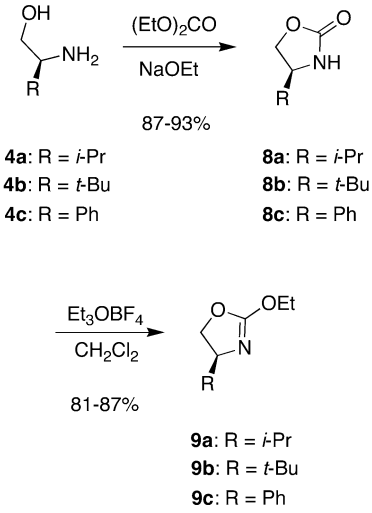
In 1986, Gawley et al. reported that ethoxyoxazolines are reactive compounds for substitution reactions with secondary amines to yield oxazolylamines.[11] Consequently, such compounds might also serve as counterparts to aminooxazolines **5** in the coupling step toward aza-bis(oxazolines) **2**. To test the feasibility of this proposal, we prepared ethoxyoxazolines **9** in a simple two-step synthesis starting from amino alcohols following literature precedent (Scheme 2).[12]

Indeed, simple stirring of aminooxazolines **5** and ethoxyoxazolines **9** in refluxing toluene in the presence of catalytic amounts of *p*-toluenesulfonic acid gave rise to the previously reported aza-bis(oxazolines) **2a** and **2b**. Isolation of the ligands by chromatography proved to be much easier than by our initial synthesis due to fewer byproducts, resulting in the case of **2b** in greatly improved yield. Moreover, the phenyl substituted aza-bis(oxazoline) **2c**, which is especially interesting in light of the great utility of the corresponding phenyl substituted bis(oxazoline) ligands,[13] was inaccessible by our original route, but now could be prepared for the first time. Due to the lability of this ligand, the reaction temperature had to be lowered to 50 °C, allowing the isolation of **2c** still in only 35% yield but in very pure form. Finally, this route also offers the possibility to synthesize mixed aza-bis(oxazolines) with two different substituents as demonstrated with the synthesis of **2d**. In the case of **2b**−**d**, crystalline material can be obtained by recrystallization from acetone, allowing their convenient storage and usage.

SCHEME 1. Synthesis of Aza-bis(oxazolines)[5]



SCHEME 2. Synthesis of Ethoxyoxazolines 8[12]



The reaction most likely proceeds through an intermediate **10**, which subsequently eliminates ethanol to give rise to **2** as the only tautomer that was observed (Scheme 3, Table 1).

(8) Reviews: (a) Reiser, O. *Chimica Oggi* **2002**, *20*, 73−76. (b) Jönssen, C.; Hallman, K.; Andersson, H.; Stemme, G.; Malkoch, M.; Malmström, E.; Hult, A.; Moberg, C. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1857−1861. (c) Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 10, 3467−3493.

(9) (a) Wittekind, R. R.; Rosenau, J. D.; Poos, G. I. *J. Org. Chem.* **1961**, *26*, 444−446. (b) Poos, G.; Carson, J.; Rosenau, J.; Roszkowski, A.; Kelley, N.; McGowin, J. *J. Med. Chem.* **1963**, *6*, 266−272.

(10) For the synthesis of aza-bis(benzoxazoles) from chlorobenzoxazoles and amines, see: Plampin, J. N.; Sam, J. *J. Pharm. Sci.* **1964**, *53*, 538−544.

(11) Gawley, R. E.; Hart, G.; Goicochea-Pappas, M.; Smith, A. L. *J. Org. Chem.* **1986**, *51*, 3076−3078.

(12) (a) Rein, K.; Goicochea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, A. L.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211−2217. (b) Tietze, L. C.; Schneider, C.; Grote, A. *Chem. Eur. J.* **1996**, *2*, 139−148.

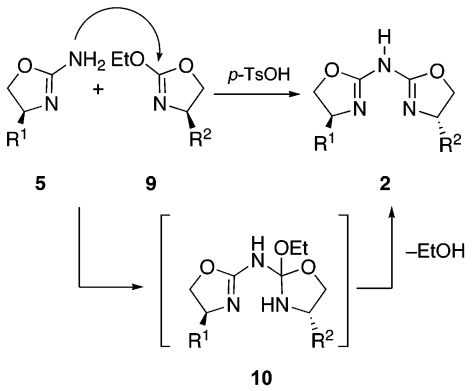
(13) For examples see: (a) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995−2997. (b) Thorhauge, J.; Roberson, M.; Hazall, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888−1898. (c) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879−2882. (d) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757. (e) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. (f) Sibi, M. P. *Curr. Org. Chem.* **2001**, *5*, 719. (g) Evans, D. A.; Johnson, J. S.; Olhava, E. J.; *J. Am. Chem. Soc.* **2000**, *122*, 1635.

TABLE 1. Synthesis of Aza-bis(oxazolines) 2 from 5 and 9

entry[a]	amino-oxazoline	ethoxy-oxazoline	Azabox	R^1	R^2	*T* (°C)	yield[b] (%)	yield (ref 5)
1	**5a**	**9a**	**2a**	*i*-Pr	*i*-Pr	reflux	51	53
2	**5b**	**9b**	**2b**	*t*-Bu	*t*-Bu	reflux	92	58
3	**5c**	**9c**	**2c**	Ph	Ph	50	35	0
4	**5b**	**9c**	**2d**	*t*-Bu	Ph	50	64	*c*

[a] All reactions were performed in toluene. 1.2 equiv of **9** and 1.0 equiv of **5** were used in the presence of catalytic amounts of *p*-TSA. [b] Determined after purification by chromatography on silica. [c] Synthesis of unsymmetrical aza(bisoxazolines) is not possible by the original protocol reported in ref 5.

SCHEME 3. Synthesis of Aza-bis(oxazolines) 2 from 5 and 9



In summary, we have developed a new protocol for the synthesis of aza-bis(oxazolines), considerably improving on yield and scope for this ligand class.

Experimental Section

General Methods. All reactions were carried out under nitrogen atmosphere in oven-dried glassware. Methylene chloride was distilled from calcium hydride. Ethanol was distilled from magnesium. Tetrahydrofuran was distilled from potassium, toluene was distilled from sodium. Amino acids were used as commercially available. The aminooxazolines **5a**−**c**,[9] oxazolidinones **8a**,**b**,[12a] oxazolidinone **8c**,[12b] and ethoxyoxazolines **9a**−**c**[11] were prepared according to literature procedures.

General Procedure for the Synthesis of Aza-bis(oxazolines). Ethoxyoxazoline **9** (6 mmol), aminooxazoline **5** (5 mmol), and a catalytic amount of *p*-toluenesulfonic acid (20 mg) were dissolved in toluene (40 mL) and heated for 24 h. After this period, the solution was concentrated in vacuo and purified by chromatography on silica using ethyl acetate/hexanes as eluent. The aza(bisoxazolines) **2b**−**d** could be recrystallized from acetone.

Bis[4,5-dihydro-(4*S*)-(1-methylethyl)-1,3-oxazol-2-yl]-amine (2a). Prepared according to the general procedure using 942 mg (6 mmol) of ethoxyoxazoline **9a** and 640 mg (5.0 mmol) aminooxazoline **5a** to yield after chromatography on silica 597 mg of **2a** (51%): R_f 0.15 (ethyl acetate/hexanes 9:1); mp 72−74 °C; $[\alpha]^{20}_D$ +118.9 (*c* 1.0, CH_3OH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.5 (br s, 1 H), 4.38 (dd, 2 H, *J* = 8.7, 8.7 Hz), 4.05 (dd, 2 H, *J* = 7.1, 8.7 Hz), 3.78−3.87 (m, 2 H), 1.65−1.79 (m, 2 H), 0.98 (d, 6 H, *J* = 6.8 Hz), 0.90 (d, 6 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 165.9, 65.6, 33.0, 18.6, 18.1; *m*/*z* (EI 70 eV) 239 (M^+); IR 3510, 3305, 3003, 1671, 1489, 1448, 1401, 1318, 1252, 1118, 960. Anal. Calcd for $C_{12}H_{21}O_2N_3$: C, 60.23; H, 8.85; N, 17.56. Found: C, 60.28; H, 8.83; N, 17.55.

Bis[4,5-dihydro-(4*S*)-(1,1-dimethylethyl)-1,3-oxazol-2-yl]-amine (2b). Prepared according to the general procedure using 1.03 g (6 mmol) of ethoxyoxazoline **9b** and 710 mg (5.0 mmol) aminooxazoline **5b** to yield after chromatography on silica 1.22 g of **2b** (92%); crystalline **2b** could be obtained by recrystallization from acetone: R_f 0.14 (ethylacetete/hexanes 9:1); mp 152−154 °C; $[\alpha]^{20}_D$ +148.6 (c 1.0, CH_3OH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.5 (br s, 1 H), 4.30 (dd, 2 H, *J* = 9.1, 9.1 Hz), 4.15 (dd, 2 H, *J* = 8.9, 6.7 Hz), 3.81 (dd, 2 H, *J* = 9.4, 6.7 Hz), 0.90 (s, 18 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 68.8, 67.4, 33.6, 20.0; *m*/*z* (EI 70 eV) 267 (M^+); IR 3528, 3193, 2989, 2879, 1762, 1674, 1599, 1481, 1450, 1406, 1370, 1257, 1061. Anal. Calcd for $C_{14}H_{25}O_2N_3$: C, 62.89; H, 9.42; N, 15.72. Found: C, 63.08; H, 9.30; N, 15.41.

Bis[4,5-dihydro-(4*S*)-phenyl-1,3-oxazol-2-yl]amine (2c). Prepared according to the general procedure at 50 °C using 1.15 g (6 mmol) of ethoxyoxazoline **9c** and 810 mg (5.0 mmol) aminooxazoline **5c** to yield after chromatography on silica 537 mg of **2c** (35%); crystalline **2c** could be obtained by recrystallization from acetone: R_f 0.17 (ethylacetete/hexanes 9:1); mp 198−201 °C; $[\alpha]^{20}_D$ +475.8 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.25 (m, 10 H), 5.13 (dd, 2 H, *J* = 9.3, 7.3 Hz), 4.72 (dd, 2 H, *J* = 9.3, 8.6 Hz), 4.18 (dd, 2 H, *J* = 8.6, 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 166.4, 141.3, 128.9, 128.2, 126.4, 73.6, 63.1; *m*/*z* (CI/ NH_3) 308.3 (MH^+); IR 3432, 3182, 3029, 2975, 2901, 1647, 1606, 1428, 1239, 1073, 390. Anal. Calcd for $C_{18}H_{17}O_2N_3$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.36; H, 5.49; N, 13.63.

[4,5-Dihydro-(4*S*)-(1,1-dimethylethyl)-1,3-oxazol-2-yl][4,5-dihydro-(4*S*)-phenyl-1,3-oxazol-2-yl]amine (2d). Prepared according to the general procedure at 50 °C using 1.15 g (6 mmol) of ethoxyoxazoline **9c** and 710 mg (5.0 mmol) aminooxazoline **5b** to yield after chromatography on silica 918 mg of **2d** (64%); crystalline **2d** could be obtained by recrystallization from acetone: R_f 0.15 (ethylacetete/hexanes 9:1); mp 130−132 °C; $[\alpha]^{20}_D$ +281.9 (*c* 0.75, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5 H), 5.18 (dd, 1 H, *J* = 9.54, 7.34 Hz), 4.63 (dd, 1 H, *J* = 9.54, 8.37 Hz), 4.39 (t, 1 H, *J* = 9.11 Hz), 4.25 (dd, 1 H, *J* = 9.09, 5.63 Hz), 4.09 (dd, 1 H, *J* = 8.35, 7.36 Hz), 3.76 (dd, 1 H, *J* = 9.12, 5.63 Hz); ^{13}C NMR ($CDCl_3$) δ 166.9, 165.9, 143.2, 128.7, 127.6, 126.5, 73.4, 67.6, 66.1, 65.8, 33.4, 25.1; N, 14.38; *m*/*z* (CI/ NH_3) 288.2 (MH^+); IR 3262, 2956, 1636, 1589, 1386, 1068, 761, 700. Anal. Calcd for $C_{16}H_{21}O_2N_3$: C, 66.92; H, 7.31; N, 14.63. Found: C, 66.70; H, 7.25.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (RE948/5-1), the International Qualitynetwork Medicinal Chemistry (DAAD/BMBF), and the Fond der chemischen Industrie.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of aza-bis(oxazolines) **2a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0350920