Synthesis of a Bifunctional Ligand for the Sequential Enantioselective Catalysis of Various Reactions

Rita Annunziata,[a] Maurizio Benaglia,*[a] Mauro Cinquini,[a] and Franco Cozzi[a]

Keywords: Asymmetric catalysis / Bifunctional ligands / Chiral ligands / Cyclopropanations / Dihydroxylations

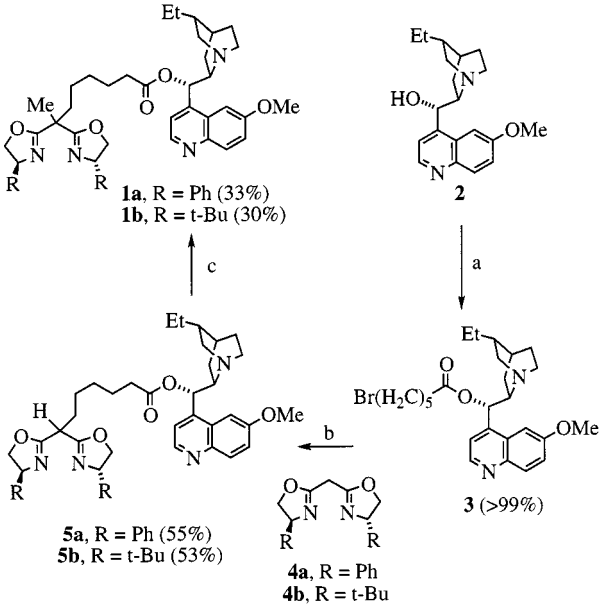
A new bifunctional ligand capable of promoting various enantioselective catalytic transformations has been prepared by connecting a bis(oxazoline) to dihydroquinidine via a spacer. This ligand has been employed in a one-pot procedure, in which the asymmetric cyclopropanation and dihydroxylation of styrene were accomplished in a sequential fashion with good enantioselectivity.

Enantioselective catalytic transformations represent invaluable tools in modern organic synthesis.[1] Many of these processes are dependent on the use of chiral ligands that, in combination with various metals, promote highly stereoselective reactions. Some ligands can be employed in a variety of processes. For instance, metal complexes of chiral bis(oxazoline)s (box)[1] have been used in enantioselective Diels−Alder, hetero Diels−Alder, and 1,3-dipolar cycloadditions, in cyclopropanations and aziridinations, in Mukaiyama-aldol and Mukaiyama−Michael additions, in allylations, hydrocyanations, and hydrosilylations of carbonyl compounds, and in reduction and oxidation reactions.[2]

In principle, further extension of the versatility of box ligands might be achieved by attaching such species to a residue capable of exerting stereocontrol over other catalytic transformations. This approach would also provide the appealing opportunity of using the new bifunctional ligand in sequential processes.[3−8]

With this goal in mind, the bis(oxazoline)−dihydroquinidine (box-DHQD) adducts **1a**,**b** were synthesized (Scheme 1). Esters and ethers of DHQD **2** have been shown to be powerful ligands for the asymmetric dihydroxylation[9] and aminohydroxylation[10] reactions developed by Sharpless. Moreover, compounds structurally related to DHQD have been employed in other enantioselective catalytic processes,[11] including alkylations, epoxidations, Michael additions, and β-lactam syntheses.[12]

Reaction of **2** with 6-bromohexanoyl chloride in the presence of triethylamine gave ester **3** in quantitative yield. This was reacted[13] with the metalated box ligands **4a** (R = Ph) and **4b** (R = *t*Bu) to afford compounds **5a**,**b** in yields of 55% and 53%, respectively. Since disubstitution at the bridging carbon atom of box ligands has proved to be essential to achieve a high degree of stereocontrol in many box-promoted reactions,[2] **5a**,**b** were methylated to give the adducts **1a**,**b** in yields of 33% and 30% (47% and 45% based on recovered **5a**,**b**), respectively.[14] It is important to note



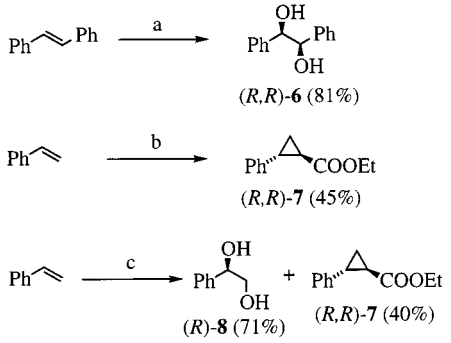
Scheme 1. Synthesis of box-DHQD ligands **1a**,**b**
Reagents and conditions: (a) $Br(CH_2)_5COCl$, Et_3N, CH_2Cl_2, room temp., 15 h; (b) metalation of **4a**,**b**: 1.0 mol equiv. of BuLi, 0.5 mol equiv. of $(iPr)_2NH$, 1.0 mol equiv. of TMEDA, THF/1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidone (DMPU) 1:3, −50 °C, 30 min; then **4a** or **4b** (1.0 mol equiv.); −50 °C, 2.0 h; alkylation: 1.0 mol equiv. of **2**, −50 °C to room temp., 15 h; (c) metalation: as in (b) on 1.0 mol equiv. of **5a**,**b**; alkylation: 1.6 mol equiv. of MeI, −50 °C to room temp., 56 h

that the bridging carbon atom in box ligands **1a**,**b** is not stereogenic since it bears two identical residues.

When compounds **1a**,**b** were employed as ligands in the Os^{VIII}-catalyzed asymmetric dihydroxylation of stilbene (Scheme 2),[15] 1,2-diphenyl-1,2-ethanediol **6** was obtained in racemic form. However, when the dihydroxylation reaction was carried out using **1b** pre-complexed with an equimolar amount of $CuBr_2$, (*R*,*R*)-**6** was formed in 81% yield with 90% enantiomeric excess (*ee*).[15] This result suggested that the box moiety can compete with the DHQD part of **1** in the osmium complexation, thereby affecting the stereoselectivity of the dihydroxylation, and that the undesired complexation is prevented by providing **1** with a metal for box ligation.

[a] Centro CNR and Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano,
Via Golgi 19, 20133 Milano, Italy

 © WILEY-VCH Verlag GmbH, 69451 Weinheim, 2001 1434−193X/01/0306−1045 $ 17.50+.50/0



Scheme 2. Stereoselective reactions promoted by ligands **1a**,**b** Reagents and conditions: (a) 1.0 mol equiv. of stilbene, 3.0 mol equiv. of $K_3Fe(CN)_6$ and K_2CO_3, 0.022 mol equiv. of K_2OsO_4 dihydrate, 0.056 mol equiv. of **1a** or **1b**, 0.058 mol equiv. of $CuBr_2$, *t*BuOH/H_2O 1:1, 0 °C to room temp., 15 h; (b) 3.0 mol equiv. of styrene, 1.0 mol equiv. of ethyl diazoacetate, 0.01 mol equiv. each of CuOTf, K_2OsO_4 dihydrate, and **1b**, room temp., 48 h; (c) see text

Similarly, the use of ligands **1a**,**b** alone in the Cu^I-promoted cyclopropanation of styrene with ethyl diazoacetate[16] led to a very poor yield of racemic **7**. On the other hand, the use of **1b** pre-complexed with an equimolar amount of potassium osmate furnished (*R*,*R*)-**7** in 45% yield with 80% *ee* (*trans*/*cis* ratio 80:20).[16] As before, it would seem that the Lewis-basic bridgehead nitrogen atom of the DHQD part of **1** can interfere with the complexation of Cu^I by the box group, thereby affecting the stereoselectivity of the process. Addition of potassium osmate prevents this phenomenon.[17]

In the light of these results, a one-pot procedure was attempted in which styrene was sequentially subjected to cyclopropanation and dihydroxylation. To a mixture of **1b** (0.1 mol equiv.), CuOTf (0.1 mol equiv.), K_2OsO_4 dihydrate (0.1 mol equiv.), and styrene (2 mol equiv.) in CH_2Cl_2 at room temp., ethyl diazoacetate (1 mol equiv.) was added over a period of 12 h by means of a syringe pump. After stirring for 48 h at this temperature, the solvent was removed, the residue was redissolved in *t*BuOH/H_2O (1:1), and $K_3Fe(CN)_6$ and K_2CO_3 (3 mol equiv. each) were added at 0 °C. After stirring for 24 h at room temp., the reaction was quenched by the addition of $NaHSO_3$. After aqueous work-up and extraction with CH_2Cl_2, the crude mixture was purified by flash chromatography to afford cyclopropane (*R*,*R*)-**7** in 40% yield with 79% *ee* along with diol (*R*)-**8** in 71% yield with 70% *ee*.[18] Ligand **1b** was also recovered in 50% yield.

This experiment showed the feasibility of the sequential catalytic process, although it proceeded with levels of stereoselection slightly lower than those observed when the two reactions were carried out independently using monofunctional ligands.[19]

In conclusion, the new bifunctional ligand box-DHQD **1b**, readily synthesized from commercially available starting materials, has been successfully applied in a sequential enantioselective catalytic process involving two different reactions.

Experimental Section

General: ^1H NMR spectra were recorded at 300 MHz and were referenced to tetramethylsilane (TMS; δ = 0.00). − ^{13}C NMR spectra were recorded at 75 MHz and were referenced to the $CDCl_3$ solvent signal (δ = 77.0). − IR spectra were recorded from thin films of the samples. − Optical rotations were measured with light of the Na-D line in 1-dm cells at 23 °C.

Synthesis of DHQD 6-Bromohexanoate (3): A solution of 6-bromohexanoyl chloride (0.612 mL, 4 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of DHQD (1.304 g, 4 mmol) and triethylamine (0.72 mL, 5.2 mmol) in dry CH_2Cl_2 (20 mL) under nitrogen at room temp. After stirring for 15 h, the reaction mixture was poured into water and the organic components were extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried with sodium sulfate, the solvent was evaporated in vacuo, and the residue was purified by flash chromatography using CH_2Cl_2/MeOH (98:2) as the eluent. The product was obtained in quantitative yield (2.010 g) as a thick yellow oil. It had $[\alpha]_D^{23}$ = +80.3 (*c* = 1.28 in $CHCl_3$). − IR: $\tilde{\nu}$ = 1740, 1230, 1170 cm^{-1}. − ^1H NMR: δ = 8.68 (d, 1 H, *J* = 4.0 Hz, quinoline 2-H), 7.95 (d, 1 H, *J* = 9.2 Hz, quinoline 8-H), 7.28−7.34 (m, 3 H, remaining aromatic protons), 6.48 (d, 1 H, *J* = 7.7 Hz, CHOCO), 3.90 (s, 3 H, MeO), 3.28 (t, 2 H, *J* = 6.7 Hz, CH_2Br), 3.23 (t, 1 H, *J* = 7.0 Hz, CHN bridgehead), 2.58−2.87 (m, 4 H, CH_2NCH_2), 2.35 (t, 2 H, *J* = 7.4 Hz, CH_2COO), 1.33−1.80 (m, 14 H, 3 CH_2 of the aliphatic chain, 2 CH and 2 CH_2 of the bicyclic ring, CH_2 of ethyl group), 0.86 (t, 3 H, *J* = 7.3 Hz, CH_3CH_2). − ^{13}C NMR: δ = 172.1, 157.7, 147.3, 144.6, 143.8, 131.6, 127.0, 121.7, 118.5, 101.4, 73.1, 59.0, 55.5, 50.6, 49.7, 37.1, 34.0, 33.2, 32.2, 27.5, 27.0, 25.9, 25.3, 23.9, 23.2, 11.9. − $C_{26}H_{35}BrN_2O_3$ (503.4): calcd. C 62.02, H 7.01, N 5.56; found C 61.87, H 6.91, N 5.63.

Synthesis of box-DHQD (5b): A solution of bis(oxazoline) **4b** (0.201 g, 0.756 mmol) in a mixture of dry THF (1 mL) and DMPU (3 mL) was added dropwise to a stirred solution of BuLi (0.458 mL of a 1.5 M solution in hexanes, 0.687 mmol), diisopropylamine (0.048 mL, 0.344 mmol), and TMEDA (0.103 mL, 0.687 mmol) in a mixture of dry THF (3 mL) and DMPU (9 mL) under nitrogen at −50 °C. The mixture was stirred at this temperature for 1.5 h, in the course of which a pale-yellow solution was formed. Thereafter, a solution of bromoester **3** (0.346 g, 0.687 mmol) in a mixture of dry THF (1 mL) and DMPU (3 mL) was added, and the resulting mixture was allowed to slowly warm to room temp. Stirring was continued for 15 h. The reaction was then quenched by the addition of a saturated aqueous ammonium chloride solution. The mixture was extracted with diethyl ether (20 mL) and the remaining aqueous phase was further extracted with CH_2Cl_2 (10 mL). The combined organic phases were washed with brine (2 × 20 mL), dried with sodium sulfate, and concentrated in vacuo. Residual traces of DMPU were removed under high vacuum. The residue was purified by flash chromatography using CH_2Cl_2/MeOH (90:10) as the eluent. The product (0.251 g) was obtained in 53% yield as a thick yellow oil. It had $[\alpha]_D^{23}$ = −3.2 (*c* = 2.8 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1739, 1664 cm^{-1}. − ^1H NMR: δ = 8.75 (d, 1 H, *J* = 4.0 Hz, quinoline 2-H), 8.02 (d, 1 H, *J* = 9.0 Hz, quinoline 8-H), 7.33−7.47 (m, 3 H, remaining aromatic protons), 6.53−6.63 (m, 1 H, CHOCO), 4.07−4.17 (m, 4 H, two CH_2O of box), 3.97 (s, 3 H, MeO), 3.84−3.90 (m, 2 H, two CH*t*Bu), 3.50 [t, 1 H, *J* = 8.0 Hz, $CH(C{=}N)_2$], 3.26−3.33 (m, 1 H, CHN bridgehead), 2.66−3.00 (m, 4 H, CH_2NCH_2), 2.38 (t, 2 H, *J* = 7.4 Hz, CH_2COO), 1.27−2.16 (m, 16 H, 4 CH_2 of the aliphatic chain, 2 CH and 2 CH_2 of the

bicyclic ring, CH_2 of ethyl group), 0.93 (t, 3 H, J = 7.3 Hz, CH_3CH_2), 0.90 (s, 9 H, one of two *t*Bu), 0.86 (s, 9 H, one of two *t*Bu). − ^{13}C NMR: δ = 172.5, 164.8, 164.7, 157.9, 147.4, 145.0, 144.0, 131.8, 127.0, 121.9, 118.5, 101.4, 75.6, 75.5, 73.3, 68.8, 59.2, 55.6, 50.8, 49.9, 39.7, 37.3, 34.3, 33.7, 29.5, 28.7, 27.1, 27.0, 26.0, 25.7, 25.4, 24.6, 23.4, 12.0. − $C_{41}H_{60}N_4O_5$ (688.9): calcd. C 71.48, H 8.78, N 8.13; found C 71.67, H 8.65, N 8.29.

Synthesis of box-DHQD (5a): This compound was similarly prepared from bromoester **3** (0.346 g, 0.687 mmol) and bis(oxazoline) **4a** (0.231 g, 0.756 mmol). The product (0.401 g) was obtained in 55% yield as a thick yellow oil. It had $[\alpha]_D^{23}$ = −1.6 (c = 0.25 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1739, 1655 cm^{-1}. − ^{1}H NMR: δ = 8.73 (d, 1 H, J = 4.0 Hz, quinoline 2-H), 8.00 (d, 1 H, J = 9.0 Hz, quinoline 8-H), 7.20−7.45 (m, 13 H, remaining aromatic protons), 6.57 (d, 1 H, J = 7.3 Hz, CHOCO), 5.17−5.26 (m, 2 H, two PhC*H*), 4.58−4.72 (m, 2 H, two protons of two CH_2O of box), 4.08−4.25 (m, 2 H, two protons of two CH_2O of box), 3.95 (s, 3 H, MeO), 3.67 [t, 1 H, J = 8.0 Hz, $CH(C{=}N)_2$], 3.23−3.33 (m, 1 H, CHN bridgehead), 2.63−3.00 (m, 4 H, CH_2NCH_2), 2.28−2.45 (m, 2 H, CH_2COO), 2.00−2.13 [m, 2 H, $CH_2CH(C{=}N)_2$], 1.25−1.90 (m, 14, 3 CH_2 of the aliphatic chain, 2 CH and 2 CH_2 of the bicyclic ring, CH_2 of ethyl group), 0.92 (t, 3 H, J = 7.1 Hz, CH_3CH_2). − ^{13}C NMR: δ = 172.5, 166.2, 157.9, 147.3, 144.7, 143.9, 142.1, 131.7, 128.7, 127.6, 126.8, 126.6, 121.9, 118.5, 101.4, 75.1, 73.5, 69.6, 59.1, 55.7, 50.7, 49.9, 39.6, 37.2, 34.3, 29.6, 28.7, 27.1, 26.9, 25.9, 25.4, 24.6, 23.2, 11.9. − $C_{45}H_{52}N_4O_5$ (729.0): calcd. C 74.15, H 7.19, N 7.67; found C 74.38, H 7.31, N 7.45.

Synthesis of box-DHQD (1b): Bis(oxazoline) **5b** (0.097 g, 0.141 mmol) was metalated as described above for the metalation of **4b**. After stirring for 1.5 h at −50 °C, MeI (0.014 mL, 0.226 mmol) was added, and the mixture was stirred at the same temperature for 3 h. It was then allowed to slowly warm to room temp. and stirring was continued for 56 h. Work-up as described above gave the crude product, which was purified by flash chromatography using CH_2Cl_2/MeOH (95:5 → 90:10) as the eluent. The product (0.030 g) was obtained in 30% yield as a thick yellow oil. It had $[\alpha]_D^{23}$ = −4.0 (c = 0.33 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1737, 1660 cm^{-1}. − ^{1}H NMR: δ = 8.75 (d, 1 H, J = 4.6 Hz, quinoline 2-H), 8.02 (d, 1 H, J = 9.2 Hz, quinoline 8-H), 7.33−7.47 (m, 3 H, remaining aromatic protons), 6.53−6.63 (m, 1 H, CHOCO), 4.07−4.17 (m, 4 H, two CH_2O of box), 3.98 (s, 3 H, MeO), 3.84−3.90 (m, 2 H, two CH*t*Bu), 3.26−3.33 (m, 1 H, CHN bridgehead), 2.66−3.00 (m, 4 H, CH_2NCH_2), 2.38 (t, 2 H, J = 7.4 Hz, CH_2COO), 1.27−2.16 (m, 16 H, 4 CH_2 of the aliphatic chain, 2 CH and 2 CH_2 of the bicyclic ring, CH_2 of ethyl group), 1.48 [s, 3 H, $CH_3C(C{=}N)_2$], 0.94 (t, 3 H, J = 7.3 Hz, CH_3CH_2), 0.90 (s, 9 H, one of two *t*Bu), 0.88 (s, 9 H, one of two *t*Bu). − ^{13}C NMR: δ = 172.5, 164.8, 164.7, 157.9, 147.4, 145.0, 144.0, 131.8, 127.0, 121.9, 118.6, 101.4, 75.5, 75.3, 73.5, 68.7, 59.2, 55.6, 50.7, 49.9, 42.0, 37.3, 36.2, 34.4, 33.7, 29.3, 27.0, 26.0, 25.7, 25.4, 24.0, 23.5, 23.4, 21.4, 12.0. − $C_{42}H_{62}N_4O_5$ (703.0): calcd. C 71.76, H 8.89, N 7.97; found C 71.53, H 8.88, N 7.81.

Synthesis of box-DHQD (1a): This compound was similarly prepared from bis(oxazoline) **5a** (0.146 g, 0.200 mmol). The product (0.049 g) was obtained in 33% yield as a thick yellow oil. It had $[\alpha]_D^{23}$ = −87.6 (c = 0.51 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1720, 1650 cm^{-1}. − ^{1}H NMR: δ = 8.72 (d, 1 H, J = 4.4 Hz, quinoline 2-H), 8.02 (d, 1 H, J = 9.2 Hz, quinoline 8-H), 7.20−7.45 (m, 13 H, remaining aromatic protons), 6.80 (d, 1 H, J = 7.3 Hz, CHOCO), 5.17−5.26 (m, 2 H, two PhC*H*), 4.58−4.72 (m, 2 H, two protons of two CH_2O of box), 4.08−4.25 (m, 2 H, two protons of two CH_2O of box), 4.01 (s, 3 H, MeO), 3.28−3.38 (m, 1 H, CHN bridgehead), 2.80−3.15 (m, 4 H, CH_2NCH_2), 2.29−2.45 (m, 2 H, CH_2COO), 2.00−2.13 [m, 2 H, $CH_2CH(C{=}N)_2$], 1.25−1.90 (m, 14 H, 3 CH_2 of the aliphatic chain, 2 CH and 2 CH_2 of the bicyclic ring, CH_2 of ethyl group), 1.64 [s, 3 H, $CH_3C(C{=}N)_2$], 0.92 (t, 3 H, J = 7.1 Hz, CH_3CH_2). − ^{13}C NMR: δ = 172.0, 169.7, 157.9, 147.2, 144.7, 144.5, 142.4, 131.8, 127.9, 127.6, 126.8, 126.6, 122.3, 118.1, 101.3, 75.3, 75.2, 72.4, 69.6, 69.5, 59.0, 56.0, 50.5, 49.8, 42.6, 36.7, 34.3, 29.3, 29.3, 28.2, 27.1, 26.4, 25.3, 24.6, 24.1, 23.0, 21.6, 11.9. − $C_{46}H_{54}N_4O_5$ (743.0): calcd. C 74.36, H 7.33, N 7.54; found C 74.18, H 7.52, N 7.39.

Synthesis of Compounds 7 and 8 by Sequential Cyclopropanation and Dihydroxylation: K_2OsO_4 dihydrate (6.6 mg) was added to a stirred solution of **1b** (13 mg, 0.018 mmol) in CH_2Cl_2 (1 mL) under nitrogen. After stirring for 10 min at room temp., CuOTf·0.5C_6H_6 (4.5 mg, 0.018 mmol) was added and stirring was continued for 30 min. Freshly distilled styrene (0.041 mL, 0.36 mmol) was then added, followed by a solution of ethyl diazoacetate (0.021 mL, 0.18 mmol) in CH_2Cl_2 (1 mL), the latter being slowly added by means of a syringe pump over a period of 12 h. After stirring for 48 h at room temp., the solvent was evaporated in vacuo, the residue was taken up in a mixture of *tert*-butyl alcohol (2 mL) and water (2 mL), and the resulting suspension was cooled to 0 °C. $K_3Fe(CN)_6$ (178 mg, 0.54 mmol) and K_2CO_3 (74 mg, 0.54 mmol) were then added, and the mixture was stirred for 15 h while the temperature was allowed to rise to ambient. An excess of Na_2SO_3 was then added and the solvent was evaporated in vacuo. The residue was taken up in CH_2Cl_2, the organic phase was dried with sodium sulfate, and the solvent was evaporated in vacuo. The crude products were separated by flash chromatography using hexanes/diethyl ether mixtures as eluents (90:10, then 70:30, then 50:50). Cyclopropane **7** (11 mg) was obtained in 40% yield, diol **8** (15 mg) in 71% yield. Their ^{1}H NMR spectra were identical to those reported. Their *ee*'s were determined by comparison of the observed optical rotations {for **7**: $[\alpha]_D^{23}$ = −234 (c = 0.10 in $CHCl_3$); for **8**: $[\alpha]_D^{23}$ = −38.5 (c = 0.20 in diethyl ether)} with those reported for samples of known *ee* {for **7**: $[\alpha]_D^{23}$ = −296 (c = 0.88 in $CHCl_3$);[16] for **8**: $[\alpha]_D^{23}$ = −55.5 (c = 3.0 in diethyl ether)[20]}.

Acknowledgments

We thank the MURST (Progetto Nazionale Stereoselezione in Sintesi Organica: Metodologie e Applicazioni) and the CNR for financial support.

[1] Review: *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH Publishers, New York, **1993**.
[2] Review: A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.
[3] The possibility of performing sequential enantioselective catalytic processes has very recently been reported for the first time: H.-B. Yu, Q.-S. Hu, L. Pu, *J. Am. Chem. Soc.* **2000**, *122*, 6500−6501. In this case, the chiral ligand was a copolymer composed of BINOL and BINAP units, which stereocontrolled the addition of diethylzinc to an aldehyde function and the Ru-catalyzed hydrogenation of a ketone, both carbonyls being present within the same molecule. For recent reports on other bifunctional ligands that have been used to promote a *single* reaction, see refs.[4−7]
[4] A. P. H. J. Schenning, J. H. Lutje Spelberg, D. H. W. Hubert, M. C. Feiters, R. J. M. Nolte, *Chem. Eur. J.* **1998**, *4*, 871−880 (epoxidation of alkenes).
[5] M. P. Sibi, G. R. Cook, P. Liu, *Tetrahedron Lett.* **1999**, *40*, 2477−2480 (reduction of ketones).
[6] Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413 (hydrocyanation of ketones).
[7] For the attachment of two identical ligands to a soluble poly-

mer support, see: C. Bolm, C. L. Dinter, A. Seger, H. Höcker, J. Brozio, *J. Org. Chem.* **1999**, *64*, 5730−5731.
[8] For a recent review on multifunctional asymmetric catalysis, see: M. Shibasaki, *Chemtracts − Organic Chemistry* **1999**, *12*, 979−998.
[9] Review: D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059−1070.
[10] L. J. Goosen, H. Liu, K. Ruprecht Dress, K. B. Sharpless, *Angew. Chem. Int. Ed.* **1999**, *38*, 1080−1083, and references therein.
[11] Review: A. Nelson, *Angew. Chem. Int. Ed.* **1999**, *38*, 1583−1585.
[12] A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. H. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.
[13] A modification of a literature procedure has been employed: I. W. Davies, L. Gerena, L. Castonguay, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Chem. Commun.* **1996**, 1753−1754.
[14] These poor yields can be ascribed to the steric hindrance and relatively low acidity of the trisubstituted bridging carbon atom. The use of stronger bases or higher temperatures for the metalation resulted in extensive decomposition of the bis(oxazoline)s. Reversal of the alkylation sequence (reaction of **4** first with MeI and then with **3**) led to only low yields of **1**.
[15] This reaction was performed as described by: K. B. Sharpless, W. Amberg, M. Beller, H. Chen, Y. Kawanami, D. Lübben, E. Manoury, Y. Ogino, T. Shibata, T. Ukita, *J. Org. Chem.* **1991**, *56*, 4585−4588. Under these conditions, the use of DHQD 4-chlorobenzoate as a ligand afforded (*R,R*)-diol **6** with 99% *ee.* The use of DHQD acetate (i.e. of an aliphatic ester of DHQD as **1**) under different conditions (E. N. Jacobsen, I. Markò, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968−1970) gave the product with 94% *ee.*
[16] This reaction was performed with *gem*-dimethyl **4b** as the ligand, as described in: D. A. Evans, K. A. Worpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726−728. Under these conditions, (*R,R*)-**7** was obtained in 56% yield with 99% *ee*; the *trans*/*cis* ratio was 73:27.
[17] It is known (T. Aratani, *Pure & Appl. Chem.* **1985**, *57*, 1839−1846) that the active catalyst in the cyclopropanation reaction is a Cu^{I} rather than a Cu^{II} species. Our reaction seems to suggest that the Cu^{I}/box species can survive the presence of Os^{VI} under the experimental conditions. In a control experiment, the cyclopropanation of styrene (ref.[16]) with ethyl diazoacetate was carried out in CH_2Cl_2 with *gem*-dimethyl **4b** as the ligand in the presence of CuOTf and K_2OsO_4 dihydrate. This gave (*R,R*)-**7** in 5% yield with 99% *ee.* This result suggested that the Os^{VI} species can indeed decrease the yield of the reaction, most probably by inhibiting the catalytic cycle. This deactivation seems to be less significant in the presence of the Os ligand DHQD.
[18] Using DHQD 4-chlorobenzoate as the ligand in the dihydroxylation of styrene (see ref.[15]), (*R*)-**8** was obtained with 74% *ee.*
[19] The sequential process was not attempted using a substrate possessing two double bonds, for instance 1,4-divinylbenzene, in order to avoid the possibility of the stereocenters generated in the first reaction "intramolecularly" affecting the stereochemical course of the second reaction. On the contrary, cyclopropane **7** would seem unlikely to exert an "intermolecular" effect on the synthesis of diol **8**. Moreover, the use of a substrate with two double bonds could give rise to up to eight stereoisomeric products in the sequential process, thus greatly complicating the stereochemical analysis of the reaction course.
[20] D. Beer, R. Meuwly, A. Vasella, *Helv. Chim. Acta* **1982**, *65*, 2570−2582.

Received November 8, 2000
[O00561]