Sequential Stereoselective Catalysis: Two Single-Flask Reactions of a Substrate in the Presence of a Bifunctional Chiral Ligand and Different Transition Metals

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

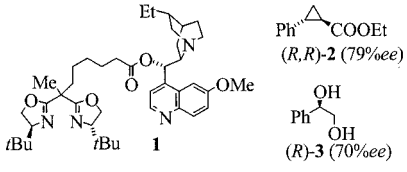
Keywords: Stereoselective catalysis / Bifunctional ligand / Chiral ligands / Cyclopropanation / Dihydroxylation

A new bifunctional ligand capable of promoting different stereoselective catalytic transformations in combination with different transition metals has been prepared by connecting with a spacer a bis(oxazoline) to dihydroquinidine; this ligand was employed in a one-flask procedure in which methyl (*E*)-3-(4-vinylphenyl)propenoate underwent first cyclopropanation at the electron-rich double bond and then dihydroxylation at the electron-poor alkene to afford a product containing four stereocenters with complete regiocontrol and high stereoselectivity.

Introduction

The possibility of performing highly stereoselective catalytic transformations at different sites of a given substrate in a sequential fashion and in a single reaction flask represents an important result, which can further improve the widespread applications of catalytic processes.[1]

In this context, we have recently reported the synthesis of the bifunctional ligand **1** (Scheme 1) containing a bis(oxazoline) moiety connected to a dihydroquinidine residue. This ligand was employed in the presence of Cu^{I} and Os^{VIII} species to promote the cyclopropanation and the dihydroxylation of different molecules of styrene in a single reaction flask. Both processes occurred with good levels of stereocontrol to afford adducts **2** and **3** in 79 and 70% *ee*, respectively.[2]

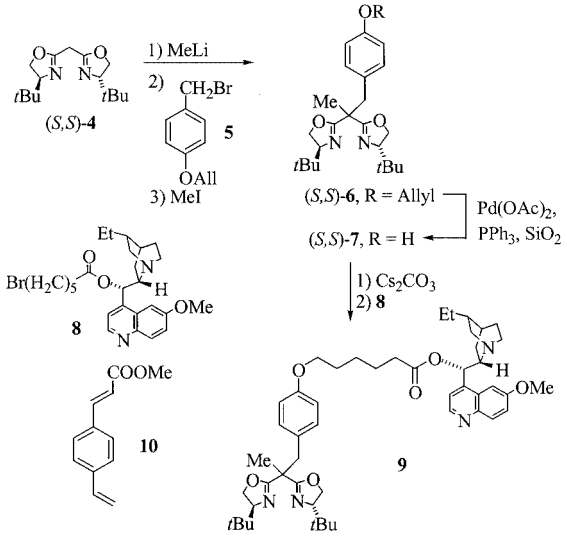


Scheme 1. Structure of ligand **1** and adducts **2** and **3**

Although this result showed the feasibility of this approach toward sequential stereoselective catalysis, we thought that the possibility of performing, in a highly regio- and stereo-controlled fashion, two one-flask reactions on a single substrate would further demonstrate its applicability.[3,4] Here, we report the results of this study.

Results and Discussion

First, we decided to synthesize a bifunctional ligand similar to **1** by a new, shorter, and more practical reaction sequence than the one previously employed.[2] We performed the synthesis of the new bis(oxazoline)-dihydroquinidine adduct **9** as described in Scheme 2.



Scheme 2. Synthesis of bifunctional ligand **9**

[a] Dipartimento di Chimica Organica e Industriale, Universita' degli Studi di Milano
Via Golgi 19, 20133 Milano, Italy
[b] CNR-ISTM, Universita' degli Studi di Milano
Via Golgi 19, 20133 Milano, Italy

Commercially available *tert*-butyl-substituted bis(oxazoline) **4** was metallated with MeLi (2.2 mol-equiv., −55 °C in THF for 1 h),[5] and alkylated first with 4-allyloxybenzyl bromide **5** (1 mol-equiv., 40 min at −10 °C) [6] then with MeI (3 mol-equiv., 15 h from −10 °C to room temp.). From this reaction, bis(oxazoline) **6** was obtained in 40% isolated yield. It must be noted that this one-pot procedure afforded **6** in better yield and a shorter time than procedures involving either methylation (or benzylation) of **4**, isolation of the monoalkylated product by chromatography, and further benzylation (or methylation). It also greatly shortened the synthesis of **6** from diethyl methylmalonate that we have recently described en route to poly(ethylene glycol)-supported bis(oxazoline)s.[6]

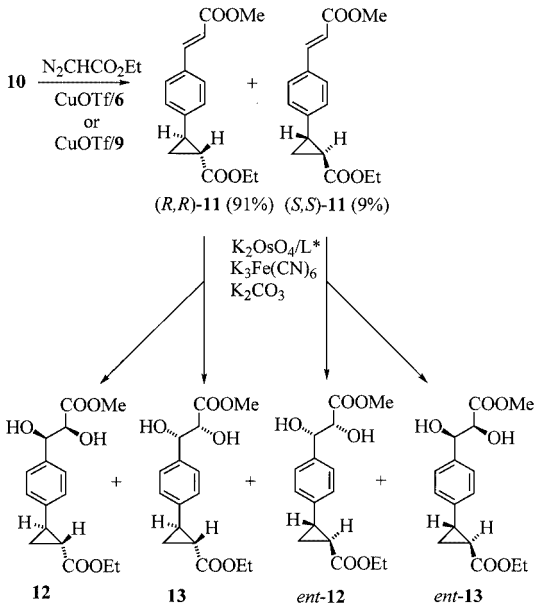
Deallylation of compound **6**, carried out at 90 °C with $Pd(OAc)_2$ and PPh_3 in EtOH in the presence of SiO_2, gave phenol **7** in 78% yield. This was then *O*-alkylated with dihydroquinidine 6-bromohexanoate (**8**)[2] in the presence of Cs_2CO_3 (DMF, 4 d, 50 °C) to afford ligand **9** in 60% yield.

As a suitable substrate for testing ligand **9**, methyl (*E*)-3-(4-vinylphenyl)propenoate (**10**) (Scheme 2) was selected, with the aim of exploiting the different electronic properties of its two double bonds to secure high regioselectivity in the first transformation. In a control experiment, it was shown that the cyclopropanation of an equimolecular mixture of styrene and methyl cinnamate with ethyl diazoacetate catalyzed by a CuOTf/bis(oxazoline) complex occurred exclusively on styrene, whereas the unsaturated ester could be quantitatively recovered. Therefore, compound **10** was prepared in 77% yield by olefination of 4-vinylbenzaldehyde under Horner−Wadsworth−Emmons conditions followed by flash-chromatographic separation to obtain the pure (*E*) isomer.

With adduct **10** in hand, we performed experiments to assess the stereoselectivity of the cyclopropanation and dihydroxylation reactions carried out in the presence of metal complexes of conventional ligands (Scheme 3). Thus, the cyclopropanation of **10** under Evans' conditions (excess ethyl diazoacetate, 0.05 mol-equiv. of CuOTf/**6**, CH_2Cl_2, room temp., 24 h) [7] afforded a *trans*/*cis* (70:30) mixture of isomers in 75% yield, as determined by ^1H NMR analysis of the crude reaction product. The *trans* isomer **11**, isolated in the pure form by flash chromatography, was shown to be constituted of a 91:9 mixture of enantiomers, to which the (*R*,*R*) and (*S*,*S*) configurations, respectively, were assigned.[8]

We then subjected the mixture of the diastereoisomerically pure adducts **11** to a dihydroxylation reaction under Sharpless' conditions (0.1 mol-equiv. of K_2OsO_4/chiral ligand complex, 3 mol-equiv. of $[K_3Fe(CN)_6]$ and K_2CO_3, *t*BuOH/water, 0 °C to room temp., 15 h)[9] using dihydroquinidine 4-chlorobenzoate as the ligand.[10] From this reaction we isolated a diol mixture in 53% yield

In principle, this mixture could be composed of four stereoisomers, namely the two diastereoisomeric diols **12** and **13**, arising from the major cyclopropane (*R*,*R*)-**11**, and their enantiomers *ent*-**12** and *ent*-**13**, deriving from (*S*,*S*)-**11**. The diastereoisomeric ratio, as determined by ^1H NMR, was



Scheme 3. Stereoselective synthesis of adducts **11**, **12**, and **13**; L*: dihydroquinidine 4-chlorobenzoate or **9**

83:17. The *ee* of the major diastereoisomer, made of **12** and *ent*-**12**, was determined to be 95%; that of the minor diastereoisomer (**13** + *ent*-**13**) was found to be 99% (*ee* established by HPLC). It must be noted that from the reaction mixture it was possible to recover the unchanged mixture of (*R*,*R*)-**11** and (*S*,*S*)-**11** in 42% yield, enriched from the originally observed 91:9 ratio (see above) up to a 96:4 ratio.

These results can be interpreted as follows. The osmylation reaction proceeds with kinetic resolution,[11] with (*S*,*S*)-**11** reacting with the Os/chiral ligand complex faster and more stereoselectively than (*R*,*R*)-**11**. The fact that **13** was obtained in higher *ee* than **12** supports this hypothesis, and suggests that the stereochemical preference of the osmium catalyst matched that of the (*S*,*S*) substrate.[12] On the basis of this reasoning and of the known stereochemical preference of the osmylation reaction of cinnamate esters promoted by dihydroquinidine-derived ligands,[9] the **12** and *ent*-**13** configurations were assigned to the largely major enantiomers of the two diastereoisomers.[13]

We then repeated the two reactions, working sequentially in one flask using compound **9** as the ligand. In this case, the order of addition of the metal species was crucial, since the basic sites of **9** can compete for the different cations involved in the process. Thus, potassium osmate was added to a solution of **9** in CH_2Cl_2, followed, after 10 min of stirring, by CuOTf.[14] As previously described,[2] this procedure allowed selective complexation of copper and osmium ions by the bis(oxazoline) and dihydroquinidine moiety of ligand **9**, respectively. The substrate **10** and ethyl diazoacetate were then added and the cyclopropanation reaction allowed to proceed for 48 h at room temperature. The solvent and the excess diazoacetate were then removed under reduced pressure, and potassium hexacyanoferrate

and potassium carbonate were added to the residue, dissolved in *t*BuOH/water, to perform the dihydroxylation reaction.[9] After overnight reaction from 0 °C to room temperature and workup, the mixture of diols featuring the *trans*-cyclopropane residue was separated from the other diols by flash chromatography and isolated in 20% yield [15] as a 75:25 mixture of (**12** + *ent*-**12**): (**13** + *ent*-**13**) diastereoisomers.[16] Their *ee* values were established by HPLC as 95 and 99% in favor of **12** and *ent*-**13**, respectively. Thus, while the diastereoselectivity of the two-flask process and of the sequential reaction were different, the *ee* in which the products have been obtained were identical, showing that the high stereocontrol characteristic of the individual bis(oxazoline) and dihydroquinidine ligands were maintained in the bifunctional ligand **9**. Remarkably, this compound could be recovered unchanged in 91% yield in the chromatographic purification of the products.

Conclusions

A bifunctional ligand capable of promoting different stereoselective catalytic transformations when coordinated to different transition metal atoms has been prepared in a simple and straightforward fashion by connecting a bis(oxazoline) to dihydroquinidine with a spacer. This ligand was employed in a one-flask procedure in which methyl (*E*)-3-(4-vinylphenyl)propenoate underwent first cyclopropanation at the electron-rich double bond and then dihydroxylation at the electron-poor alkene to afford a product containing four stereocenters with complete regiocontrol and high stereoselectivity. These results showed that multifunctional ligands can conveniently be exploited to perform a new type of stereoselective process called sequential stereoselective catalysis.

Experimental Section

General: ^{1}H NMR spectra were recorded at 300 MHz and are referenced to tetramethylsilane (TMS) at δ = 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz and are referenced to δ = 77.0 ppm in [D]chloroform ($CDCl_3$). IR spectra were recorded on thin films. Optical rotations were measured at the Na-D line in a 1-dm cell at 23 °C.

Synthesis of Ligand 9: This compound was obtained by a stepwise synthesis starting from bis(oxazoline) **4**.

Synthesis of 2,2-Bis{[(4*S*)-4-(1,1-dimethylethyl)-1,3-oxazolin-2-yl]-1-[4-(2-propenyl)oxyphenyl]propane (6): A 1.6 M solution of MeLi in Et_2O (0.520 mL, 0.826 mmol) was added dropwise to a stirred solution of bis(oxazoline) **4** (0.100 g, 0.375 mmol) in dry THF (5 mL), cooled to − 55 °C under nitrogen. After stirring at −55 °C for 1 h, 4-allyloxybenzyl bromide **5** (0.085 g, 0.375 mmol) in THF (3 mL) was added dropwise and the reaction mixture was stirred at −10 °C for 40 min. MeI (0.070 mL, 1.125 mmol) in THF (1 mL) was then added and the reaction mixture was allowed to warm to room temp. and stirred at that temperature overnight. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL) and the resulting mixture was extracted three times with 10 mL of CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography with CH_2Cl_2/EtOAc (9:1) as eluent to afford the product (0.064 g, 0.15 mmol, 40% yield) as a viscous pale-yellow oil. The product had optical rotation and spectroscopic data identical to those reported in the literature.[6]

Synthesis of 2,2-Bis{2-[(4*S*)-4-(1,1-dimethylethyl)-1,3-oxazolin-2-yl]-1-(4-hydroxyphenyl)propane (7): A solution of compound **6** (0.426 g, 1 mmol) in ethanol (10 mL), containing $Pd(OAc)_2$ (0.023 g, 0.1 mmol) and PPh_3 (0.115 g, 0.44 mmol), was refluxed for 90 min. The resulting mixture was cooled to room temp., and SiO_2 (1 g) was added in one portion. After 40 min of stirring at room temp., the mixture was filtered through a Celite plug, the solvent was evaporated under vacuum, and the residue was purified by flash chromatography with CH_2Cl_2/EtOAc (6:4) as eluent to give the product (0.301 g, 0.78 mmol, 78% yield). The product had optical rotation, m.p., and spectroscopic data identical to those reported in the literature.[6]

Synthesis of Compound 9: To a stirred solution of compound **7** (0.041 g, 0.107 mmol) in dry DMF (2 mL), warmed to 50 °C, cesium carbonate (0.244 g, 0.749 mmol) was added, followed, after 30 min, by bromide **8** (0.054 g, 0.107 mmol), dissolved in DMF (2 mL). The resulting mixture was stirred at 50 °C for 4 d, and the solvent was then removed under vacuum. The residue was taken up in CH_2Cl_2 (10 mL), the mixture was filtered, and the filtrate was concentrated under vacuum to give the crude product, which was purified by flash chromatography with CH_2Cl_2/MeOH (98:2, then 95:5, and finally 85:15) as eluent to give the product (0.052 g, 0.064 mmol, 60% yield) as a yellow viscous oil that solidified on standing in the freezer. $[\alpha]_D^{23} = -14.3$ (c = 0.48, chloroform). IR: $\tilde{\nu}$ = 1741, 1658 cm^{-1}. ^{1}H NMR: δ = 0.85 (s, 9 H, CMe_3), 0.88 (s, 9 H, CMe_3), 0.95 (t, $^3J_{H,H}$ = 4.0 Hz, 3 H, CH_2CH_3), 1.42 (s, 3 H, CH_2CCH_3), 1.51 (m, 5 H, *CH*, CH_2CH_3 and $OCH_2CH_2CH_2$), 1.53 (m, 1 H, A part of an AB system, $NCHCH_2CH$), 1.76 (m, 5 H, $OCHCH_2CH_2CH_2$ and $CHCHCH_2CH_3$), 1.80 (m, 1 H, B part of an AB system, $NCHCH_2CH$), 2.44 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2COOCH), 2.73 (m, 3 H, NCH_2CH_2CH and A part of an AB system in $NCH_2CHCH_2CH_3$), 2.90 (dd, $^3J_{H,H}$ = 7.0 and $^2J_{H,H}$ = 9.0 Hz, 1 H, B part of an AB system, $NCH_2CHCH_2CH_3$), 3.15 (A part of an AB system, $^2J_{H,H}$ = 13.7 Hz, 1 H, $ArCH_2CCH_3$), 3.31 (m, 1 H, $NCHCHOCO$), 3.33 (A part of an AB system, $^2J_{H,H}$ = 13.7 Hz, 1 H, $ArCH_2CCH_3$), 3.83 (m, 2 H, CH_2CHCMe_3), 3.88 (t, $^3J_{H,H}$ = 6.0 Hz, 2 H, $OCH_2CH_2CH_2$), 3.98 (s, 3 H, OCH_3), 4.17 (m, 4 H, CH_2CHCMe_3), 6.58 (d, $^3J_{H,H}$ = 6.8 Hz, 1 H, *CH*OCO), 6.74 (A part of an AB system, $^3J_{H,H}$ = 9.0 Hz, 2 H, aromatic hydrogen atoms), 7.08 (B part of an AB system, $^3J_{H,H}$ = 9.0 Hz, 2 H, aromatic hydrogen atoms), 7.34 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 3-H of quinoline), 7.10 (dd, $^3J_{H,H}$ = 9.2 and $^4J_{H,H}$ = 2.6 Hz, 1 H, 7-H of quinoline), 7.45 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H, 5-H of quinoline), 8.02 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, 8-H of quinoline), 8.74 (d, $^3J_{H,H}$ = 4.7 Hz, 1 H, 2-H of quinoline) ppm. ^{13}C NMR: δ = 12.0, 21.05, 23.3, 24.6, 25.4, 25.7, 25.8, 26.0, 27.1, 28.9, -33.8, 33.9, 34.4, 37.3, 41.15, 43.5, 49.9, 50.7, 55.6, 59.1, 67.4, 68.7, 73.3, 75.4, 75.6, 101.4, 113.9, 118.6, 121.9, 127.0, 128.85, 131.5, 131.8, 143.9, 144.7, 147.4, 157.7, 157.9, 167.2, 167.8, 172.5 ppm. $C_{49}H_{68}N_4O_6$ (808.53): calcd. C 72.74, H 8.47, N 6.92; found C 72.48, H 8.39, N 7.03.

Synthesis of Methyl (*E*)-3-(4-Vinylphenyl)propenoate (10): Trimethylphosphonoacetate (1.11 mL, 6.87 mmol) in THF (3 mL) was slowly added to a stirred suspension of oil-free NaH (0.165 g, 6.87 mmol) in THF (5 mL), cooled to −30 °C. After 30 min of stirring at −30 °C, 4-vinylbenzaldehyde (0.818 g, 6.2 mmol) in THF (2 mL) was added and the reaction mixture was stirred at

−30 °C for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (10 mL), the organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried with sodium sulfate, and the solvent was removed under vacuum. The residue was purified by flash chromatography with hexanes/EtOAc (95:5) as eluent to afford the pure (*E*) isomer in 77% yield (0.897 g, 4.77 mmol) as a white solid, m.p. 73−74 °C (ref.[17] 74.5−75 °C). IR: $\tilde{\nu}$ = 1711 cm^{-1}. ^1H NMR: δ = 3.78 (s, 3 H, MeO), 5.29 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, one hydrogen atom of CH=CH_2), 5.78 (d, $^3J_{H,H}$ = 15.0 Hz, 1 H, one hydrogen atom of CH=CH_2), 6.41 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, HC=CHCOOMe), 6.69 (dd, $^3J_{H,H}$ = 15.0, 8.4 Hz, 1 H, CH=CH_2), 7.38 (A part of AB system, $^3J_{H,H}$ = 8.3 Hz, 2 H, aromatic hydrogen atoms), 7.46 (B part of AB system, $^3J_{H,H}$ = 8.3 Hz, 2 H, aromatic hydrogen atoms), 7.66 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, HC=CHCOOMe) ppm. ^{13}C NMR: δ = 52.3, 112.3, 117.0, 126.2, 126.6, 135.8, 137.1, 144.0, 146.1, 170.2 ppm.

Synthesis of *trans*-Cyclopropane 11: A solution of bis(oxazoline) **6** (0.0217 g, 0.051 mmol) and CuOTf·0.5PhH (0.0126 g, 0.05 mmol) in CH_2Cl_2 (3 mL), kept under nitrogen, was stirred for 1 h at room temp. Ester **10** (0.188 g, 1 mmol) in CH_2Cl_2 (3 mL) was added to this mixture. A solution of ethyl diazoacetate (0.525 mL, 5 mmol) in CH_2Cl_2 was slowly added by means of a syringe pump. After a total of 24 h of stirring at room temp., the low-boiling materials were removed under vacuum and the residue was analyzed by ^1H NMR to assess the *trans*/*cis* diastereoisomeric ratio. The residue was then purified by flash chromatography with hexanes/EtOAc (95:5 and then 80:20) as eluent to afford the pure *trans* isomer as a colorless liquid in 52.5% yield (0.144 g, 0.525 mmol). $[\alpha]_D^{23}$ = −195.2 (*c* = 0.42, chloroform). IR: $\tilde{\nu}$ = 1723, 1712 cm^{-1}. ^1H NMR: δ = 1.30 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, $COOCH_2CH_3$), 1.34 (A part of an AB system, $^2J_{H,H}$ = 5.2, $^3J_{H,H}$ = 6.2, 9.7 Hz, 1 H, one hydrogen atom of CH_2 of cyclopropane), 1.66 (B part of an AB system, $^2J_{H,H}$ = 5.2, $^3J_{H,H}$ = 5.2, 9.3 Hz, 1 H, one hydrogen atom of CH_2 of cyclopropane), 1.95 (ddd, $^3J_{H,H}$ = 4.2, 5.2, 9.7 Hz, 1 H, Ar*CH* of cyclopropane), 2.54 (ddd, $^3J_{H,H}$ = 4.2, 6.2, 9.3 Hz, 1 H, *CH*COOEt of cyclopropane), 4.9 (s, 3 H, OCH_3), 4.18 (q, 2 H, $^3J_{H,H}$ = 7.2 Hz, 2 H, $COOCH_2CH_3$), 6.42 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, *HC*=CHCOOEt), 7.27 (A part of an AB system, $^3J_{H,H}$ = 8.3 Hz, 2 H, aromatic hydrogen atoms), 7.46 (B part of an AB system, $^3J_{H,H}$ = 8.3 Hz, 2 H, aromatic hydrogen atoms), 7.67 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, HC=*CH*COOEt) ppm. ^{13}C NMR: δ = 14.2, 17.6, 24.5, 26.0, 51.7, 60.8, 117.3, 126.6, 128.2, 130.0, 143.0, 144.3, 168.0 ppm. $C_{16}H_{18}O_4$ (274.16): calcd. C 70.05, H 6.61; found C 69.89, H 6.71. The *ee* was determined by HPLC as 93:7 [DAICEL Chiralpack OD-H, hexane/*i*PrOH (85:15), flow rate 0.8 mL/min, λ = 210 nm, t_R = 7.38 min (minor) and 8.57 min (major)].

Synthesis of Diols 12 and 13. Two-Flask Reaction: Quinidine 4-chlorobenzoate (0.024 g, 0.051 mmol), dissolved in *t*BuOH/water (1:1, 2 mL), was added to a cooled (0 °C) and stirred solution of cyclopropane **11** (0.139 g, 0.51 mmol) in the same solvent (3 mL), followed by K_2OsO_4 dihydrate (0.019 g, 0.051 mmol), $[K_3Fe(CN)_6]$ (0.504 g, 1.53 mmol), and K_2CO_3 (0.211 g, 1.53 mmol). The mixture was stirred at 0 °C for 6 h and then at room temp. for 9 h. Excess solid sodium sulfite was then added, and the mixture was stirred for 30 min. The organic solvent was removed under vacuum, and the aqueous solution was extracted with CH_2Cl_2 (3 × 5 mL) and EtOAc (2 × 5 mL). The combined organic phases were dried and concentrated under vacuum, and the residue was purified by flash chromatography with hexanes/EtOAc (70:30 and then 50:50) as eluent. The product, a white viscous oil, was isolated in 53% yield as an 83:17 mixture of diastereoisomers (see text). $[\alpha]_D^{23}$ = −34.0 (*c* = 0.42, chloroform). IR: $\tilde{\nu}$ = 3350, 1742 cm^{-1}. ^1H NMR of the major diastereoisomer: δ = 1.32 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, $COOCH_2CH_3$), 1.33 (m, 1 H, one hydrogen atom of CH_2 of cyclopropane), 1.62 (dt, $^3J_{H,H}$ = 5.8, 8.7 Hz, 1 H, one hydrogen atom of CH_2 of cyclopropane), 1.95 (ddd, $^3J_{H,H}$ = 4.2, 5.8, 8.3 Hz, 1 H, *CH*Ar of cyclopropane), 2.56 (ddd, $^3J_{H,H}$ = 4.2, 6.2, 8.7 Hz, 1 H, *CH*COOEt of cyclopropane), 2.67 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, *HO*-CHAr), 3.08 (d, $^3J_{H,H}$ = 6.2 Hz, 1 H, *HO*CHCOOMe), 3.85 (s, 3 H, OCH_3), 4.21 (q, 2 H, $^3J_{H,H}$ = 7.2 Hz, 2 H, $COOCH_2CH_3$), 4.38 (dd, $^3J_{H,H}$ = 2.8 and 6.2 Hz, 1 H, HO*CH*COOMe), 5.02 (dd, $^3J_{H,H}$ = 2.8 and 7.2 Hz, 1 H, HO*CH*Ar), 7.13 (A part of an AB system, $^3J_{H,H}$ = 8.2 Hz, 2 H, aromatic hydrogen atoms), 7.34 (B part of an AB system, $^3J_{H,H}$ = 8.2 Hz, 2 H, aromatic hydrogen atoms) ppm. ^{13}C NMR of the major diastereoisomer: δ = 14.4, 17.5, 22.2, 27.1, 53.4, 61.1, 74.2, 75.0, 126.7, 129.9, 138.5, 142.0, 171.5, 174.2 ppm. ^1H NMR of the minor diastereoisomer: δ = 1.03 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, $COOCH_2CH_3$), 1.33 (m, 1 H, one hydrogen atom of CH_2 of cyclopropane), 1.71 (dt, $^3J_{H,H}$ = 5.8, 7.4 Hz, 1 H, one hydrogen atom of CH_2 of cyclopropane), 2.10 (ddd, $^3J_{H,H}$ = 4.2, 5.8, 8.3 Hz, 1 H, *CH*Ar of cyclopropane), 2.53 (ddd, $^3J_{H,H}$ = 4.2, 6.2, 7.4 Hz, 1 H, *CH*COOEt of cyclopropane), 2.67 (br. s, 1 H, one *OH*), 3.10 (br. s, 1 H, other *OH*), 3.84 (s, 3 H, OCH_3), 3.91 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, $COOCH_2CH_3$), 4.37 (br. s, 1 H, HO*CH*-COOMe), 5.00 (br. s, 1 H, HO*CH*Ar), 7.14 (A part of an AB system, $^3J_{H,H}$ = 8.2 Hz, 2 H, aromatic hydrogen atoms), 7.33 (B part of an AB system, $^3J_{H,H}$ = 8.2 Hz, 2 H, aromatic hydrogen atoms) ppm. ^{13}C NMR of the minor diastereoisomer: δ = 14.4, 17.5, 24.2, 26.4, 53.3, 60.6, 74.1, 74.7, 126.2, 126.7, 137.1, 142.5, 170.0, 173.5 ppm. $C_{16}H_{20}O_6$ (308.16): calcd. C 62.33, H 6.54; found C 62.69, H 6.48. The *ee* was determined by HPLC [DAICEL Chiralpack AD, hexane/*i*PrOH (80:20), flow rate 0.8 mL/min, λ = 220 nm; for the major diastereoisomer: t_R of **12** (major) = 18.36 min; t_R of *ent*-**12** (minor) = 17.29 min; for the minor diastereoisomer: t_R of *ent*-**13** = 14.43 min (only enantiomer detected].

Synthesis of Diols 12 and 13. One-Flask Reaction: K_2OsO_4 dihydrate (0.0188 g, 0.051 mmol) was added to a stirred solution of ligand **9** (0.041 g, 0.051 mmol) in CH_2Cl_2 (2.5 mL). After 10 min of stirring at room temp., CuOTf·0.5C_6H_6 (0.0126 g, 0.05 mmol) was added, and stirring was continued for 30 min. Compound **10** (0.094 g, 0.5 mmol), dissolved in CH_2Cl_2 (1 mL), was then added, followed by ethyl diazoacetate (0.263 mL, 2.5 mmol) in CH_2Cl_2 (1 mL), the latter being slowly added by a syringe pump over a period of 12 h. After 48 h of stirring at room temp., the solvent was evaporated under vacuum, the residue was dissolved in a 1:1 mixture of *tert*-butanol (2 mL) and water (2 mL), and the resulting suspension was cooled to 0 °C. $K_3Fe(CN)_6$ (0.493 g, 1.5 mmol) and K_2CO_3 (0.207 g, 1.5 mmol) were then added, and the mixture was stirred at 0 °C for 6 h and at room temp. 9 h. Excess solid sodium sulfite was then added, and the mixture was stirred for 30 min. The organic solvent was removed under vacuum, and the aqueous solution was extracted with CH_2Cl_2 (3 × 5 mL) and EtOAc (2 × 5 mL). The combined organic phases were dried and concentrated under vacuum, and the residue was purified by flash chromatography with hexanes/EtOAc (90:10, then 70:30, and finally 50:50) as eluent. The diols featuring the *trans*-configured cyclopropane residue were isolated in 20% yield (0.031 g, 0.1 mmol) as a 75:25 mixture of diastereoisomers (see text). These were analyzed for *ee* determination as described above and mentioned in the text. Further elution of the crude reaction product with CH_2Cl_2/MeOH (90:10) as eluent allowed us to recover the ligand **9** in 91% yield.

Acknowledgments

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

[1] Review: *Comprehensive Asymmetric Catalysis*, vol. I−IV (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[2] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, *Eur. J. Org. Chem.* **2001**, 1045−1048.

[3] The possibility of performing sequential stereoselective catalytic processes was reported for the first time using a copolymeric catalyst by: [3a] H.-B. Yu, Q.-S. Hu, L. Pu, *J. Am. Chem. Soc.* **2000**, *122*, 6500−6501. For more recent results obtained with supported ligands see: [3b] B. M. Choudary, N. S. Chowdary, S. Madhi, M. N. Kantam, *Angew. Chem. Int. Ed.* **2001**, *40*, 4620−4623. [3c] B. M. Choudary, N. S. Chowdary, K. Jyothi, N. S. Kumar, M. N. Kantam, *Chem. Commun.* **2002**, 586−587; and references therein.

[4] For reviews describing related approaches see: [4a] M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989−1999 ("asymmetric two-center catalysis"). [4b] G. J. Rowlands, *Tetrahedron* **2001**, *57*, 1865−1882 ("ambifunctional cooperative catalysis").

[5] M. I. Burguete, J. M. Fraile, J. I. Garcia, E. Garcia-Verdugo, C. I. Herrerias, S. V. Luis, J. A. Mayoral, *J. Org. Chem.* **2001**, *66*, 8893−8901,

[6] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, M. Pitillo, *J. Org. Chem.* **2001**, *66*, 3160−3166.

[7] D. A. Evans, K. A. Worpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726−728.

[8] The assignment was tentatively based on the assumption that the enantiofacial preference of the Evans' cyclopropanation reaction was the same for **10** and styrene; it must be noted that (*R*,*R*)-**11** and the major *trans* adduct obtained from styrene both had strong negative optical rotations.

[9] H. Kwong, C. Sorato, Y. Ogino, H. Chen, K. B. Sharpless, *Tetrahedron Lett.* **1990**, *31*, 2999−3002.

[10] We are well aware of the fact that other ligands (e.g. PHAL-DHQD) secure higher stereoselectivity in this reaction. Nevertheless, we considered dihydroquinidine 4-chlorobenzoate a good structural analog of ligand **9**.

[11] For previous examples of asymmetric dihydroxylation reactions proceeding with kinetic resolution see: [11a] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, F. Ponzini, *Biorg. Med. Chem. Lett.* **1993**, *11*, 2397−2402. [11b] M. S. VanNieuwenhze, K. B. Sharpless, *J. Am. Chem. Soc.* **1993**, *115*, 7864−7865. [11c] E. J. Corey, M. C. Noe, A. Guzman-Perez, *J. Am. Chem. Soc.* **1995**, *117*, 10817−10824.

[12] For a general treatment of double stereoselection and the definition of matched and mismatched pairs see: S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1−30.

[13] On the basis of these stereochemical results it could be anticipated that a ligand such as **9** prepared starting from either bis(oxazoline) **4** and dihydroquinine or (less practically) from *ent*-**4** and dihydroquinidine would provide a more stereoselective overall process in which the stereochemical preference of the osmylation reaction matches that of the cyclopropane substrate **11**.

[14] The possibility that CuOTf is oxidized to catalytically inactive Cu^{II} species by the Os^{VI} salt has previously been considered and found to be negligible (see ref.[2]).

[15] This yield is only slightly lower than that calculated for the mixture of the *trans*-cyclopropanediols obtained performing the reactions separately (27.8%). In a control experiment the reactions were repeated sequentially in one flask, operating as described in the case of **9**, and using bis(oxazoline) **6** and dihydroquinidine 4-chlorobenzoate as the ligands. From this experiment the *trans*-cyclopropanediols were isolated in 21% yield as an 80:20 mixture of diastereoisomers.

[16] As suggested by one referee, in the cyclopropanation reaction the active catalyst may bind to a molecule of substrate via the osmate, and it would be cleaved on addition of water in the second step.

[17] DE Patent 2340601, **1973**, *Chem. Abstr.* **1973**, *80*, 145713.

Received November 25, 2002
[O02661]