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Tetrahedron: *Asymmetry* 14 (2003) 765–771

TETRAHEDRON: *ASYMMETRY*

New bis(oxazoline) ligands with secondary binding sites for the asymmetric cyclopropanation of furans

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Received 6 December 2002; accepted 14 January 2003

Abstract—The diastereo- and enantioselective cyclopropanation of furans was achieved in up to 91% *ee* using a new set of chiral bis(oxazoline) ligands that are able to use secondary binding sites to enhance selectivity. In contrast, with substrates such as styrene and *N*-Boc-pyrrole, with which no secondary interactions with the ligands can occur, only moderate selectivities (<50% *ee*) were achieved. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The concept of C_2-symmetry has proved to be invaluable for asymmetric catalysis.[1] Among the vast number of ligands known, the most successful ones such as the binaphthyls[2] or the bisoxazolines[3] contain a C_2-symmetry axis, and only a few notable exceptions such as phosphinooxazolines[4] or ferrocenyl ligands[5] are equally effective chiral inductors.

In a C_2-symmetrical chiral catalyst two diagonally opposite quadrants are sterically blocked, which allows the unambiguous side approach of a *trans*-alkene in copper-catalyzed, asymmetric carbene and nitrene transfer reactions following the model proposed by Pfaltz (Fig. 1a)[6] for semicorrin ligands and the experimental data available.[7] In contrast, the approach of a *cis*-alkene is ambiguous if R and R^1 are similar in their steric volume, which should result in a less effective differentiation of the enantiotopic faces of the double bond (Fig. 1b),[7b] being reflected in only limited success in the asymmetric cyclopropanation of such substrates to date.[8] However, if the sterically blocking substituent in the ligand could form an *attractive* interaction to one of the substituents of the *cis*-alkene, its selective recognition might become possible (Fig. 1c). The concept of molecules being able to interact with substrates by means of secondary interactions is long known from enzymes, but has only recently led to the successful development of unnatural ligands for asymmetric catalysis.[9]

2. Results and discussion

2.1. Preparation of the ligands

In order to test this concept in the cyclopropanation of alkenes, we synthesized the bisoxazoline **1a** according

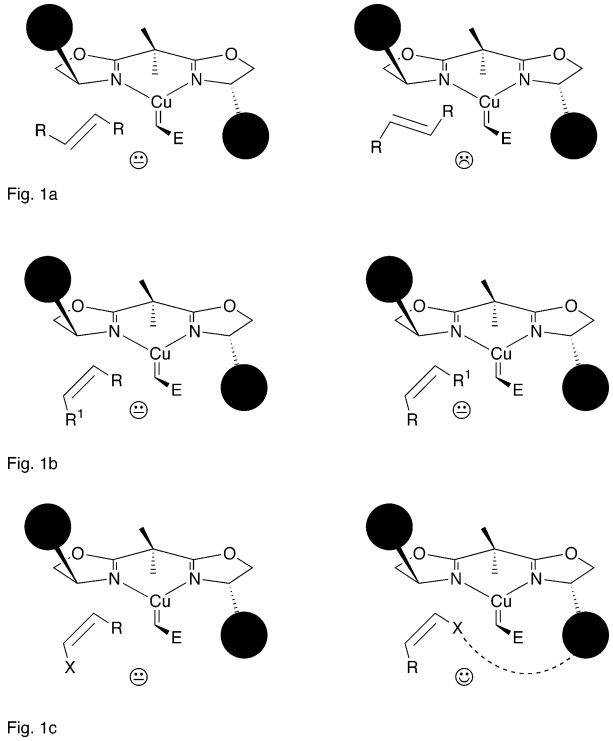

Figure 1. Model for cyclopropanation of alkenes with copper(I) bis(oxazoline) complexes.

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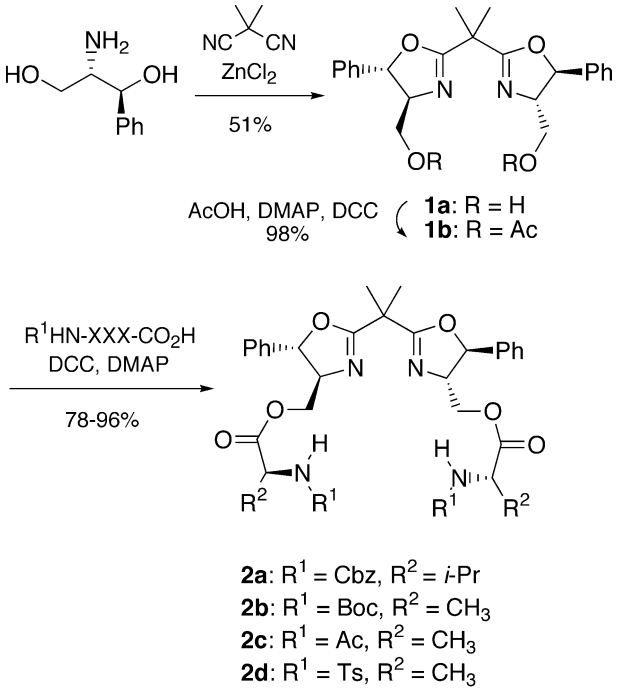
doi:10.1016/S0957-4166(03)00094-6

to literature precedent.[10,11] It was felt that **1a** would be a suitable starting ligand as it would allow further attachment of side chains with the possibility of exerting a secondary interaction with a substrate. Indeed, **1a** was readily acylated with carboxylic acids by the method of Steglich,[12] giving rise to **1b** and the protected α-amino acid containing ligands **2** (Scheme 1).



Scheme 1.

2.2. Asymmetric cyclopropanation of styrene

To benchmark our new set of ligands, we first tested some of them in the copper(I)-catalyzed cyclopropanation of styrene (Table 1). Not too surprisingly, only moderate enantioselectivities were observed (<50% *ee*) since the substituents blocking substrate approach are not particularly sterically demanding[13] (ligands **1a** and **1b**). Moreover, the side groups of ligands **2** are quite flexible, such that they can interfere with the approach of the substrate in the void quadrants, as evidenced by the decrease in selectivity switching from **1** to **2**.

2.3. Asymmetric cyclopropanation of 2,3-dihydrofuran

We next investigated the asymmetric cyclopropanation of 2,3-dihydrofuran (Table 2), which should also be a poor substrate on the basis of the steric arguments put forward above, but offers the possibility of hydrogen bonding with the ligand through the oxygen of the furan ring.

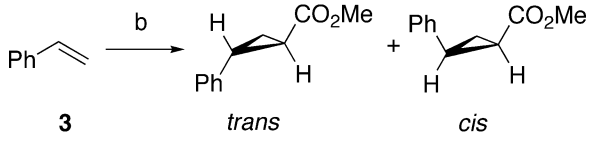
Nevertheless, the obtained diastereo- and enantioselectivities were disappointingly low as well (<40% *ee* in all cases), however, molecular modeling studies confirmed that the furan oxygen cannot interact with the ligand side chains for steric reasons. Moreover, it is important to note that with all of the substrates described, the selectivities changed little in reactions with the different ligands **1** and **2**.

2.4. Asymmetric cyclopropanation of furans

Furan itself gave very poor results for the cyclopropanation with diazoacetates in the presence of ligands **1** and **2**. Only moderate enantioselectivities (<50% *ee*) and especially very low yields (<20%) did not encourage us to investigate this substrate in more detail. However, the situation changed dramatically when methyl furancarboxylates **5** were subjected to cyclopropanation with our ligands (Table 3).[14,15]

In all cases, cyclopropanation took place at the lesser substituted (presumably more electron-rich) double

Table 1. Cyclopropanation of styrene **3** with methyl diazoacetate[a]

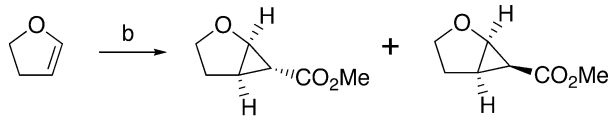


3 *trans* *cis*

Entry	Ligand	Yield[c] (%)	*trans*:*cis*[d]	*trans*[e] % ee	*cis*[e] % ee
1	**1a**	60	60:40	42	49
2	**1b**	61	61:39	46	58
3	**2b**	67	58:42	21	35

[a] All reactions were carried out under nitrogen.
[b] Cu(I)-ligand (1 mol%), N_2CHCO_2Me, CH_2Cl_2, rt, 12 h.
[c] Isolated yields.
[d] Determined by ^1H NMR.
[e] Determined by GC analysis using Chrompack CP-Chirasil DEX CB column.

Table 2. Cyclopropanation of 2,3-dihydrofuran **4** with methyl diazoacetate[a]



4 *exo* *endo*

Entry	Ligand	Yield[c] (%)	*exo*:*endo*[d]	*exo*[e] % ee	*endo*[e] % ee
1	**1a**	63	82:18	15	12
2	**1b**	41	84:16	18	25
3	**2a**	43	83:17	25	36
4	**2b**	66	80:20	25	37

[a] All reactions were carried out under nitrogen.
[b] Cu(I)-ligand (1 mol%), N_2CHCO_2Me, CH_2Cl_2, rt, 12 h.
[c] Isolated yields.
[d] Determined by ^1H NMR.
[e] Determined by GC analysis using Macherey Nagel Lipodex E column.

bond, yielding the *exo*-adduct **6** exclusively. Using the ligand **1a**, **6a**-Me was already obtained with respectable 69% *ee* (Table 2, entry 1). Taking into account the relatively small steric requirements of the CH_2OH-groups, as suggested in the experiments using **3** and **4** as substrates, the hydroxy groups might act as hydrogen donors, interacting with the carbomethoxy group in **5a** as a hydrogen acceptor. This could constrain **5a**, consequently limiting its degrees of freedom to approach the metal center of the catalyst (Fig. 2).

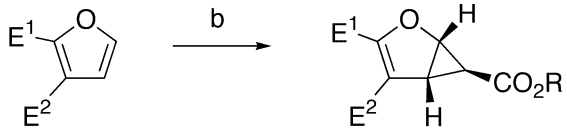
In accordance with this model, the enantioselectivity for **6a**-Me dropped significantly to 45% *ee* (Table 3, entry 2) if the ligand **1b** was used in which the possibility for hydrogen donation was removed. Moreover, using ligands **2** the enantioselectivity was further increased. With these ligands, hydrogen donation could be possible through the amino groups in the amino acid side chain. Accordingly, the selectivities were highest with the ligands containing the strongest hydrogen donors. Thus, switching from **2b** (R^1 = *tert*-butoxycarbonyl) via **2c** (R^1 = acetyl) to **2d** (R^1 = tosyl) the enantioselectivity for **6a** increased from 77–83% *ee* to 88–91% *ee* (Table 3, entries 4–8). Switching from **6a** to **6b** (entries 9 and 10), in which the ester group is moved out by one carbon, the selectivity dramatically decreases again, which is consistent with the proposal that secondary interactions from the ligand are less efficient in these cases.

2.5. Asymmetric cyclopropanation of *N*-Boc-pyrrole

When *N*-Boc-pyrrole **7** was used as a substrate the enantioselectivities obtained were again low in all cases (Table 4), which further supports our reasoning that secondary interactions might play a decisive role in governing the selectivity of the cyclopropanation of **5**.

With **7**, hydrogen bonding might be possible through the carbonyl oxygen of the *N*-Boc group. However, the steric bulk of this group impedes such an interaction with the ligand. Consequently, the selectivities were poor and the product *ee* did not exceed 50%. Most

Table 3. Cyclopropanation of methyl furan-2-carboxylate **5** with ethyl and methyl diazoacetate[a]



5a: $E^1 = CO_2Me$, $E^2 = H$
5b: $E^1 = H$, $E^2 = CO_2Me$

6a-R
6b-R

Entry	Substrate	R	Ligand	Yield[c] (%)	**6**[d] % ee
1	**5a**	Me	**1a**	45	69
2	**5a**	Me	**1b**	46	45
3	**5a**	Me	**2a**	41	62
4	**5a**	Me	**2b**	43	77
5	**5a**	Me	**2d**	39	88
6	**5a**	Et	**2b**	42	83
7	**5a**	Et	**2c**	33	85
8	**5a**	Et	**2d**	36	91[e]
9	**5b**	Et	**2b**	31	68
10	**5b**	Et	**2d**	19	40

[a] All reactions were carried out under nitrogen.
[b] Cu(I)-ligand (2 mol%), N_2CHCO_2R, CH_2Cl_2, rt, 12 h.
[c] Isolated yields.
[d] Determined by HPLC using Daicel Chiralcel OD-H column.
[e] 99% *ee* after recrystallization from pentane.

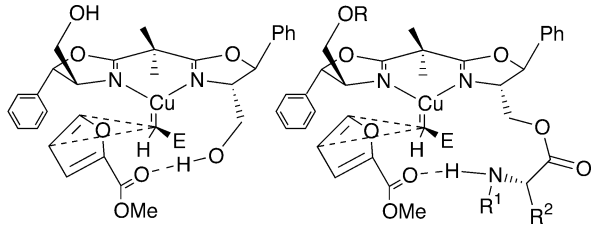
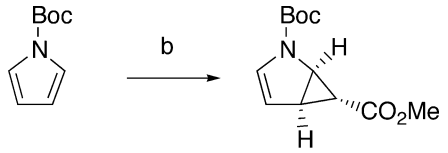


Figure 2.

Table 4. Cyclopropanation of *N*-Boc-pyrrole **7** with methyl diazoacetate[a]



7 **8**

Entry	Ligand	Yield[c] (%)	**8**[d] % *ee*
1	**1a**	52	46
2	**1b**	50	22
3	**2a**	57	28
4	**2b**	48	34
5	**2c**	46	27

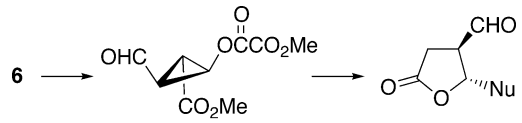
[a] All reactions were carried out under nitrogen.
[b] Cu(I)-ligand (1.5 mol%), N_2CHCO_2Me, CH_2Cl_2, rt, 12 h.
[c] Isolated yields.
[d] Determined by HPLC using Daicel Chiralcel OD-H column.

importantly, **7** is cyclopropanated predominantly with *opposite* diastereofacial selectivity to **5**,[16] indicating that the approach of **7** is indeed controlled by steric hindrance with the *N*-Boc group (cf. Fig. 1b; **7**: $R^1 = N$-Boc; R = CH; **5**: $R^1 = O$; R = CH). Unfortunately, methyl pyrrole-2-carboxylates, being analogous to the furan **6a**, failed to undergo cyclopropanation with our ligands, preventing further comparison between furans and pyrroles in this transformation.

3. Conclusion

In conclusion, the new ligands **2** effect the enantioselective cyclopropanation of **5a**, in which hydrogen bonding as a secondary interaction from the ligands to the substrate appears to control the selectivity, as was suggested by control experiments with ligands **1** and substrates **3**, **4**, **5b** and **7**.

Furthermore, the cyclopropanation of **5a** seems to be useful for the stereoselective synthesis of γ-butyrolactones **10**, which have been used as precursors for paraconic acids (Scheme 2). Cyclopropane **6a**-Et can be obtained in enantiopure form by a single recrystallization from pentane. Ozonolysis of **6** leads to the trisubstituted aldehyde **9** which upon addition of nucleophiles and base triggered saponification of the oxalic ester followed by a retroaldol-lactonization cascade, gives rise to *trans*-disubstituted γ-butyrolactones **10** in good yields.[16a,17]



9 **10**

Scheme 2.

4. Experimental

4.1. General remarks

Reactions with moisture-sensitive chemicals were performed under nitrogen in a flame-dried reaction flask. Solvents were dried by standard methods.

Chromatography was completed using Macherey-Nagel silica gel (0.03–0.06 mm). Enantiomeric excesses were determined by analytical HPLC using a 'Chiracel OD-H' column (50×4.6 mm, 10 μm, flow: 1 ml/min, 20°C) and a UV detector at 254 nm. TLC analysis was completed using commercially pre-coated aluminium sheets 60 F 254 (Merck). Melting points (uncorrected) were obtained using a Büchi SMP 20 machine. IR spectra were obtained using Mattson Genesis series Perkin Elmer 298 FT-IR and Bruker IFS 66 machines, ν values are reported in units of cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded using Bruker ARX 400, Avance 300 and AC 250 F machines with δ values reported in ppm and J values reported in Hz. Multiplicities were determined by DEPT (distortionless enhancement by polarization transfer) measurements. MS were recorded on Finnigan MAT 95 and Varian MAT 311A machines. Elemental analyses were completed using a Heraeus CHN-Rapid machine. XRD analyses were obtained with a Stoe Imaging Plate System, Siemens Stoe AED2. Optical rotation values were obtained using a Perkin–Elmer polarimeter PE 241.

4.2. Ligand synthesis

4.2.1. 2,2-Bis[(4*S*,5*S*)-4-hydroxymethyl-5-phenyl-1,3-oxazolin-2-yl]propane, 1a. $ZnCl_2$ (79.9 mg, 0.59 mmol, 6 mol%) was melted at 0.1 Torr and subsequently allowed to cool to rt under a nitrogen atmosphere. (1*S*,2*S*)-(+)-2-amino-1-phenylpropane-1,3-diol (4.93 g, 29.5 mmol) and 2,2-dimethyl-malononitrile (0.92 g, 9.77 mmol) in chlorobenzene (30 ml) were added and the mixture was heated under reflux for 24 h. After cooling to room temperature the mixture was filtered and concentrated. The residue was dissolved in CH_2Cl_2 (30 ml) and extracted with water (3×20 ml), and the combined aqueous phases were extracted once with CH_2Cl_2 (30 ml). The combined organic layers were dried (Na_2SO_4) and concentrated, the residue was purified by silica chromatography (EtOAc/MeOH 10:1). The product obtained this way was further purified by refluxing in diethyl ether to yield 1.97 g (51%) **1a** as colorless crystals. $R_f = 0.34$ (EtOAc/MeOH 10:1). Mp = 157–158°C; $[\alpha]_D^{20}$ −86.0 (c 1.00, CH_2Cl_2); IR (KBr): $\nu = 3329$, 3004, 3000, 2946, 2923, 2868, 1651, 1497, 1459, 1389, 1273, 1239, 1151, 1117, 1091, 974, 952, 935, 894, 763, 699 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, D_2O-exchange): $\delta = 1.69$ (s, 6H, CH_3), 3.64 (dd, $J = 11.9$, 3.0 Hz, 2H, CH_2OH), 3.96 (dd, $J = 11.9$, 2.6 Hz, 2H, CH_2OH), 4.11 (ddd, $J = 6.2$, 3.0, 2.6 Hz, 2H, H-4), 5.54 (d, $J = 6.2$ Hz, 2H, H-5), 7.25–7.41 (m, 10H, Ph-H); ^{13}C NMR (62 MHz, $CDCl_3$): $\delta = 23.86$ (+, CH_3), 39.74 (C_{quat}, $C(CH_3)_2$), 63.99 (−, CH_2OH), 75.87 (+, CHPh), 83.39 (+, $CHCH_2OH$), 125.57 (+, Ph-C), 128.38 (+, Ph-C), 128.85 (+, Ph-C), 140.51 (C_{quat}, Ph-C), 171.12 (C_{quat},

C-2); MS (EI): m/z (%) = 394 (2) [M^+], 364 (42) [M^+–CH_2OH], 219 (100), 91 (11). $C_{23}H_{26}N_2O_4$ (394.47): calcd: C, 70.03; H, 6.64; N, 7.10; found: C, 69.7; H, 6.57; N, 6.95%.

4.2.2. General procedure for the coupling of carboxylic acids with 1a (GP1). To the carboxylic acid (2.1 equiv.) in CH_2Cl_2 was added with stirring 4-dimethylaminopyridine (DMAP, 2.8 equiv.) and the bis(oxazoline) **1a** (1.0 equiv.). *N*,*N*′-Dicyclohexylcarbodiimide (DCC, 2.3 equiv.) was added during 5 min at 0°C, followed by stirring for 15–20 h at rt. After filtration, the solution was concentrated, and the residue was purified on silica.

4.2.3. Acetic acid 2-[1-((4*S*)-acetoxymethyl-(5*S*)-phenyl-4,5-dihydro-oxazol-2-yl)-1-methyl-ethyl]-(5*S*)-phenyl-4,5-dihydro-oxazol-(4*S*)-ylmethyl ester, 1b. Bis(oxazoline) **1a** (100 mg, 0.25 mmol, 1.0 equiv.), acetic acid (33 mg, 0.53 mmol, 2.1 equiv.), DMAP (87 mg, 0.71 mmol, 2.8 equiv.) and DCC (119 mg, 0.58 mmol, 2.3 equiv.) in CH_2Cl_2 (10 ml) were reacted according to GP1. Purification by chromatography on silica (CH_2Cl_2/EtOH 40:1) yielded **1b** as a colorless oil (118 mg, 98%): R_f = 0.52 (CH_2Cl_2/EtOH 20:1); $[\alpha]_D^{20}$ −22.1 (*c* 1.0, CH_2Cl_2); IR (Neat): ν = 3033, 2985, 2940, 1744, 1658, 1456, 1384, 1237, 1149, 1124, 1041, 977, 960, 760, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.69 (s, 6H, CH_3), 2.03 (s, 6H, $COCH_3$), 4.21–4.35 (m, 6H, 4(4′)-H and CH_2), 5.26 (d, J = 6.2 Hz, 2H, 5(5′)-H), 7.23–7.33 (m, 10H, Ph-H); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.65 (+, CH_3CO), 24.71 (+, CH_3), 39.19 (C_{quat}, $C(CH_3)_2$), 65.45 (–, CH_2), 73.62 (+, C-5(5′)), 84.27 (+, C-4(4′)), 125.77, 128.42 and 128.78 (+, Ph-C), 140.11 (C_{quat}, Ph-C), 170.10 (C_{quat}, C-2(2′)), 170.65 (C_{quat}, $COCH_3$); MS (EI): m/z (%) = 478.4 (80, M^+), 418.3 (62, M^+–CH_3COOH), 405.4 (64, M^+–CH_3COOH-CH_2), 261.2 (59), 186.1 (23), 158.0 (22), 155.0 (20), 133.9 (40), 90.9 (26), 69.0 (28), 43.1 (100). $C_{27}H_{30}N_2O_6$ (478.55): calcd: C, 67.77; H, 6.32; N, 5.85; found: C, 67.98; H, 6.32; N, 5.83%.

4.2.4. (2*S*)-Benzyloxycarbonylamino-3-methyl-butyric acid 2-{1-[(4*S*)-((2*S*)-benzyloxycarbonyl-amino-3-methyl-butyryloxymethyl)-(5*S*)-phenyl-4,5-dihydro-oxazol-2-yl]-1-methyl-ethyl}-(5*S*)-phenyl-4,5-dihydro-oxazol-(4*S*)-ylmethyl ester, 2a. Bis(oxazoline) **1a** (500 mg, 1.27 mmol, 1.0 equiv.), *N*-Cbz-*L*-valin (668 mg, 2.66 mmol, 2.1 equiv.), DMAP (433 mg, 3.55 mmol, 2.8 equiv.) and DCC (601 mg, 2.91 mmol, 2.3 equiv.) in CH_2Cl_2 (10 ml) were reacted according to GP1. Purification on silica (CH_2Cl_2/EtOH 40:1) yielded 940 mg (86%) **2a** as a colorless foam: R_f = 0.29 (CH_2Cl_2/EtOH 30:1); mp = 56–57°C; $[\alpha]_D^{20}$ −36.5 (*c* 1.31, CH_2Cl_2); IR (KBr): ν = 3300, 3095, 2936, 2851, 1740, 1690, 1645, 1465, 1320, 1153, 1120, 970, 752, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.81 (d, J = 6.8 Hz, 6H, $CH(CH_3)_2$), 0.90 (d, J = 6.8 Hz, 6H, $CH(CH_3)_2$), 1.66 (s, 6H, $C(CH_3)_2$), 2.03–2.21 (m, 2H, $CH(CH_3)_2$), 4.25–4.41 (m, 8H, H-4, CH_2OCO, CHNHCbz), 5.10 (s, 4H, CH_2Ph), 5.27–5.33 (m, 4H, H-5, NH), 7.29–7.34 (m, 20H, Ph-H); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 17.57 (+, $CH(CH_3)_2$), 18.96 (+, $CH(CH_3)_2$), 24.61 (+, $C(CH_3)_2$), 31.29 (+, $CH(CH_3)_2$), 39.22 (C_{quat}, $C(CH_3)_2$), 59.20 (+, CHNHCbz), 65.91 (–, CH_2OCO, CH_2Ph), 67.07 (–, CH_2OCO, CH_2Ph), 73.05 (+, $CHPh$), 84.02 (+, $CHCH_2O$), 125.86 (+, Ph-C), 127.53 (+, Ph-C), 128.10 (+, Ph-C), 128.17 (+, Ph-C), 128.53 (+, Ph-C), 128.86 (+, Ph-C), 136.33 (C_{quat}, Ph-C), 139.96 (C_{quat}, Ph-C), 156.18 (C_{quat}, CO_2CH_2Ph), 170.15 (C_{quat}, C-2), 171.82 (C_{quat}, $COCHNHZ$); MS (FAB) (NBA/CH_2Cl_2): m/z (%) = 1722.8 (100) [$2MH^+$], 861.6 (100) [MH^+]. $C_{49}H_{56}N_4O_{10}$ (861.00): calcd: C, 68.36; H, 6.56; N, 6.51; found: C, 68.11; H, 6.72; N, 7.45%.

4.2.5. (2*S*)-*tert*-Butoxycarbonylamino-propionic acid 2-{1-[(4*S*)-((2*S*)-*tert*-butoxycarbonylaminopropionyloxymethyl)-(5*S*)-phenyl-4,5-dihydro-oxazol-2-yl]-1-methyl-ethyl}-(5*S*)-phenyl-4,5-dihydro-oxazol-(4*S*)-ylmethyl ester, 2b. Bis(oxazoline) **1a** (497 mg, 1.26 mmol, 1.0 equiv.), *N*-Boc-alanine (501 mg, 2.65 mmol, 2.1 equiv.), DMAP (431 mg, 3.53 mmol, 2.8 equiv.) and DCC (598 mg, 2.90 mmol, 2.3 equiv.) in CH_2Cl_2 (20 ml) were reacted according to GP1. Purification on silica (CH_2Cl_2/EtOH 40:1) yielded 895 mg (96%) **2b** as a colorless foam: mp: 63–65°C; R_f = 0.31 (CH_2Cl_2/EtOH 20:1). $[\alpha]_D^{20}$ −48.8 (*c* 1.0 in CH_2Cl_2). IR (KBr): ν = 3377, 2981, 2937, 1747, 1712, 1657, 1520, 1456, 1390, 1367, 1252, 1165, 1120, 1068, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, J = 7.2 Hz, 6H, CH_3-CH-NHBoc), 1.44 (s, 18H, Boc-CH_3), 1.68 (s, 6H, CH_3), 4.25–4.44 (m, 8H), 5.05–5.07 (m, 2H, NH), 5.29–5.31 (m, 2H, 5,5′-H), 7.27–7.30 (m, 10H, Ph-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.51 (+, CH_3-CH-NHBoc), 24.55 (+, CH_3), 28.27 (+, $C(CH_3)_3$), 39.13 (C_{quat}), 49.14 (+, CH_3-CH-NHBoc), 65.71 (–, CH_2), 73.44 (+, C-5(5′)), 79.85 (C_{quat}, $C(CH_3)_3$), 83.80 (+, C-4(4′)), 125.83, 128.52 and 128.82 (+, Ph-C), 139.89 (C_{quat}, Ph-C), 155.02 (C_{quat}, OCON), 170.13 (C_{quat}, C-2(2′)), 173.13 (C_{quat}, CO_2); MS (FAB) (NBA/CH_2Cl_2): m/z (%) = 737.6 (100, MH^+), 215.3 (12). $C_{39}H_{52}N_4O_{10}$ (736.86): calcd: C, 63.57; H, 7.11; N, 7.60; found: C, 63.43; H, 7.22; N, 7.85%.

4.2.6. (2*S*)-Acetylamino-propionic acid 2-{1-[(4*S*)-((2*S*)-acetylamino-propionyloxymethyl)-(5*S*)-phenyl-4,5-dihydro-oxazol-2-yl]-1-methyl-ethyl}-(5*S*)-phenyl-4,5-dihydro-oxazol-(4*S*)-yl-methyl ester, 2c. **1a** (250 mg, 0.63 mmol, 1 equiv.), *N*-Ac-alanine (169 mg, 1.29 mmol, 2.0 equiv.), DMAP (198 mg, 1.62 mmol, 2.6 equiv.) and DCC (305 mg, 1.48 mmol, 2.3 equiv.) in CH_2Cl_2 (15 ml) were reacted according to GP1. Purification on silica (CH_2Cl_2/EtOH 30:1) yielded 307 mg (78%) **2c** as a colorless foam: R_f = 0.32 (CH_2Cl_2/MeOH 30:1). Mp = 58–60°C; $[\alpha]_D^{20}$ −32.6 (*c* 1.07, CH_2Cl_2); IR (KBr): ν = 3299, 2977, 2927, 1747, 1710, 1649, 1533, 1444, 1366, 1255, 1145, 1078, 700, 689 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (d, J = 7.2 Hz, 6H, CH_3CHNHAc), 1.68 (s, 6H, CH_3), 1.97 (s, 6H, CH_3CO), 4.25–4.43 (m, 6H), 4.55–4.64 (m, 2H), 5.23–5.32 (m, 2H, H-5), 6.26–6.29 (m, 2H, NH), 7.24–7.38

(m, 10H, Ph-H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=18.37$ (+, CH_3CHNHAc), 23.00 (+, C(CH_3)$_2$), 24.67 (+, CH_3CO), 39.23 (C_{quat}, $C(CH_3)_2$), 48.04 (+, CH_3CHNHAc), 65.77 (–, CH_2), 73.47 (+, CHPh), 83.75 (+, $CHCH_2O$), 125.84 (+, Ph-C), 128.64 (+, Ph-C), 128.93 (+, Ph-C), 139.91 (C_{quat}, Ph-C), 170.21 (C_{quat}, C-2), 172.85 (C_{quat}, $COCH_3$, CO_2), 172.98 (C_{quat}, $COCH_3$, CO_2); MS (FAB) (NBA/CH_2Cl_2): m/z (%)= 621.4 (100) [MH$^+$], 508.4 (38). $C_{33}H_{40}N_4O_8$ (620.70): calcd: C, 63.86; H, 6.50; N, 9.03; found: C, 64.05; H, 6.71; N, 8.76%.

4.2.7. (2*S*)-Tosylamino-propionic acid 2-{1-[(4*S*)-((2*S*)-tosylaminopropionyloxymethyl)-(5*S*)-phenyl-4,5-dihydro-oxazol-2-yl]-1-methyl-ethyl}-(5*S*)-phenyl-4,5-dihydro-oxazol-(4*S*)-ylmethyl ester, 2d. Bis(oxazoline) **1a** (487 mg, 1.24 mmol, 1.0 equiv.), *N*-tosylalanine (634 mg, 2.61 mmol, 2.1 equiv.), DMAP (424 mg, 3.47 mmol, 2.8 equiv.) and DCC (588 mg, 2.85 mmol, 2.3 equiv.) in CH_2Cl_2 (20 ml) were reacted according to GP1. Purification on silica (CH_2Cl_2/EtOH 40:1) yielded 860 mg (82%) **2b** as a colorless foam: mp: 69–70°C; $R_f=0.26$ (CH_2Cl_2/EtOH 40:1). $[\alpha]_D^{20}$ −31.6 (*c* 1.0, CH_2Cl_2); IR (KBr): $\nu=3280$, 3064, 2987, 2939, 1747, 1655, 1456, 1336, 1165, 1146, 1093, 976, 700, 663 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=1.30$ (d, $J=7.2$ Hz, 6H, CH_3-CH-NHTs), 1.69 (s, 6H, CH_3), 2.33 (s, 6H, Ts-CH_3), 3.96–4.26 (m, 8H, 4(4′)-H, CH_2 and CH_3-CH-NHTs), 5.08 (d, $J=6.5$ Hz, 2H, NH), 5.64 (d, $J=8.9$ Hz, 2H, 5(5′)-H), 7.15–7.34 (m, 16H, Ph-H), 7.68–7.75 (m, 4H, Ph-H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta=19.62$ (+, CH_3-CH-NHTs), 21.42 (+, Ts-CH_3), 24.73 (+, CH_3), 39.23 (C_{quat}), 51.63 (+, CH_3-CH-NHTs), 65.83 (–, CH_2), 73.44 (+, C-5(5′)), 83.62 (+, C-4(4′)), 125.62, 127.23, 128.68, 128.97 and 129.66 (+, Ph-C and Ts-C), 137.16 (C_{quat}, Ts-C), 139.88 (C_{quat}, Ph-C), 143.57 (C_{quat}, Ts-C), 170.26 (C_{quat}, C-2(2′)), 171.96 (C_{quat}, CO); MS (FAB) (NBA/ CH_2Cl_2): m/z (%)=1690.7 (100, 2MH$^+$), 845.5 (100, MH$^+$). $C_{43}H_{48}N_4O_{10}S_2$ (845.01): calcd: C, 61.12; H, 5.73; N, 6.63; found: C, 60.98; H, 5.90; N, 6.62%.

4.3. Asymmetric cyclopropanation

4.3.1. General procedure for the cyclopropanation of alkenes (GP2). A mixture of the ligand **1** or **2** (0.032 mmol) and Cu(OTf)$_2$ (0.024 mmol) in 2 ml of CH_2Cl_2 was stirred for about 30 min at room temperature before one drop of phenylhydrazine ($\approx$15 μl) and the alkene (7 mmol) was added. The light brown mixture was stirred for about 5 min. A solution of alkyl diazoacetate (1.5 mmol) in 10 ml of CH_2Cl_2 was added dropwise at room temperature during 12 h. The reaction mixture was filtered through a short pad of basic alumina and the solvent was evaporated in vacuo. The residue was purified on silica to provide the product.

4.3.2. (1*S*,5*S*,6*S*)-(−)-2-Oxa-bicyclo[3.1.0]hex-3-ene-3,6-dicarboxylic acid 6-ethyl ester 3-methyl ester 6a-Et. Using GP2, 115 mg (36%) of **6a**-Et were obtained from **5a** with ligand **2d** as a colorless oil. HPLC analysis (Chiracel OD-H, hexane/ethanol 99:1, 1.0 ml/min): 91% *ee*, rt 16.7 min (1*R*,5*R*,6*R*)-isomer, 19.7 min (1*S*,5*S*,6*S*)-isomer. R_f (hexanes/EE 5:1)=0.14. Recrystallization at −30°C from pentane yielded colorless crystals (99% *ee*): mp 42°C; $[\alpha]_D^{20}$ −272 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=1.16$ (dd, $J=2.7$, 1.1 Hz, 1H, 6–H), 1.23 (t, $J=7.1$ Hz, 3H, CH_3), 2.87 (ddd, $J=5.3$, 2.9, 2.7 Hz, 1H, 5-H), 3.78 (s, 3H, OCH_3), 4.12 (q, $J=7.1$ Hz, 2H, CH_2), 4.97 (dd, $J=5.3$, 1.1 Hz, 1H, 1-H), 6.39 (d, $J=2.9$ Hz, 1H, 4-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $d=14.2$ (+, CH_3), 21.5 (+, C-6), 31.9 (+, C-5), 52.1 (+, OCH_3), 61.0 (–, CH_2), 67.5 (+, C-1), 116.0 (+, C-4), 149.3 (C_{quat}, C-3), 159.5 (C_{quat}, CO), 171.7 (C_{quat}, CO); IR (KBr): $\tilde{\nu}=3118$, 2956, 1720, 1617, 1428, 1380, 1297, 1166, 1124, 1041, 954, 831, 725 cm^{-1}; MS (70 eV, EI): m/z (%)=212.1 [M^+] (9.8), 153.0 [M^+–CO_2Me] (11.5), 139.0 [M^+–CO_2Et] (100), 124.9 (24.4), 98.9 (28.6), 96.9 (31.7), 78.9 (11.3), 59.0 (13.5), 52.1 (11.5). $C_{10}H_{12}O_5$ (212.2): calcd: C, 56.60; H, 5.70; found: C, 56.51; H, 5.73%.

4.3.3. (1*S*,5*R*,6*S*)-2-Oxa-bicyclo[3.1.0]hex-3-ene-4,6-dicarboxylic acid 6-ethyl ester-3-methyl ester (6b-Et). According to GP2 (9 mmol **5b**, 3 mmol ethyl diazoacetate) with ligand **2b** (2 mol%), 210 mg (31%) were obtained as a yellow oil. HPLC analysis (Chiracel OD-H, hexane/ethanol 99.7:0.3, 1.0 ml/min): 68% *ee*, rt 18.45 min (1*R*,5*S*,6*R*), 24.50 min (1*S*,5*R*,6*S*). $[\alpha]_D^{20}$ −272 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=1.14$ (ddd, $J=2.9$, 1.0, 0.5 Hz, 1H, 6-H), 1.27 (t, $J=7.1$ Hz, 3H, CH_3), 3.10 (ddd, $J=5.7$, 2.9, 0.5 Hz, 1H, 5-H), 3.77 (s, 3H, CH_3), 4.15 (q, $J=7.1$ Hz, 2H, CH_2), 5.02 (ddd, $J=5.7$, 1.0, 0.9 Hz, 1H, 1-H), 7.21 (ddd, $J=0.9$, 0.6, 0.5 Hz, 1H, 3-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta=14.2$ (+, CH_3), 21.7 (+, C-5), 29.5 (+, C-6), 51.4 (+, CH_3), 61.0 (–, CH_2), 68.9 (+, C-1), 156.3 (+, C-3), 164.0 (C_{quat}, CO), 171.4 (C_{quat}, CO); IR (neat): $\tilde{\nu}=3109$, 2986, 2957, 1730, 1604, 1031; MS (EI, 70 eV): m/z (%)=212.2 (12) [M^+], 184.1 (11), 139.1 (100), 127.1 (16), 126.1 (11), 111.1 (129), 108.1 (18), 107.1 (24), 99.1 (61), 95.1 (13), 83.1 (11), 79.1 (15), 58.1 (16), 43.1 (64), 29.1 (36). $C_{10}H_{12}O_5$ (212.2): calcd: C, 56.60; H, 5.70; found: C, 56.64; H, 5.58%.

4.3.4. 2-Azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylic acid 2-*tert*-butyl ester 6-methyl ester, 8. Using GP2 (7 mmol **7**, 2.4 mmol methyl diazoacetate) with ligand **1a** (1.5 mol%), 298 mg (52%) were obtained as a yellow oil. HPLC analysis (Chiracel OD, hexane/ethanol 99:1, 1.0 ml/min): 46% *ee*, rt 1.1 min (1*R*,5*R*,6*R*)-isomer, 1.8 min (1*S*,5*S*,6*S*)-isomer. ^{1}H NMR (250 MHz, $CDCl_3$, signal doubling because of rotamers) δ 0.92 (br s, 1H), 1.46 (s, 9H), 2.77 (br s, 1H), 3.62 and 3.65 (s, 3H), 4.26–4.40 (m, 1H), 5.28–5.36 (m, 1H), 6.40–6.55 (br s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, signal doubling because of rotamers) δ 22.62 and 22.76, 28.11, 30.91 and 32.16, 44.06 and 44.19, 51.72, 81.61, 109.78, 129.55 and 129.74, 150.84 and 151.14, 173.23 and 173.50; MS (DCI(NH_3)) 257 (100) [M++NH_3+H]; $C_{12}H_{17}NO_4$ (239.3): calcd: C, 60.24; H, 7.16; found: C, 60.46; H, 7.17%.

Acknowledgements

Financial Support of the Deutsche Forschungsgemeinschaft (SPPP1118, Re 948/5-1) and the Fonds der Chemischen Industrie as well as generous gifts of chemicals by Degussa AG are gratefully acknowledged.

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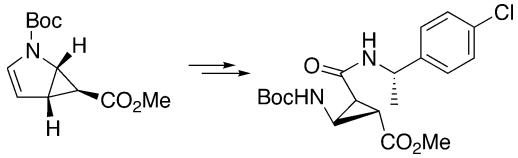

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