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Novel C_2-symmetric bisoxazolines with a chiral *trans*-(2*R*,3*R*)-diphenylcyclopropane backbone: preparation and application in several enantioselective catalytic reactions

Yaşar Gök, Timothy Noël, Johan Van der Eycken *

Laboratory for Organic and Bioorganic Synthesis, Department of Organic Chemistry, Ghent University, Krijgslaan 281 (S.4), B-9000 Ghent, Belgium

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ABSTRACT

Various chiral bisoxazoline ligands with a chiral *trans*-(2*R*,3*R*)-diphenylcyclopropane backbone have been efficiently synthesized (five examples). These chiral ligands were tested and compared in palladium(0)-catalysed enantioselective allylic alkylations (up to 97% ee), copper(I)-catalysed enantioselective cyclopropanations (up to 89% ee) and aziridinations (up to 90% ee). We observed that the presence of a stereogenic centre on the oxazoline moiety is mandatory in order to obtain acceptable enantioselectivities.

1. Introduction

Nitrogen-containing ligands are known as inexpensive, easily accessible and stable alternatives to phosphane ligands.[1] As a result, the design, synthesis and application of a wide variety of nitrogen ligands have received much attention, for example, semicorrins,[2] diimines,[3] salen,[4] 2,2′-bipyridines,[5] amidines,[6] sulfoximines[7] and, recently, imidates with an exocyclic coordinating nitrogen.[8] However, bisoxazoline (BOX) ligands have received the greatest share of attention.[9] Due to their wide applicability, metal complexes based on C_2-symmetric BOX ligands have been established as an interesting class of privileged stereodirecting ligands in asymmetric catalysis.[10] Since their initial report, a lot of research has been devoted towards the synthesis and application of these BOX ligands. The majority of these ligands are derived from optically active β-amino alcohols in order to produce an oxazoline ring with a stereogenic centre next to the coordinating nitrogen. Although a large variety of enantiomerically pure amino alcohols are readily available, the most successful systems are generally derived from phenylglycinol or *tert*-leucinol.

The BOX ligand **1**, which has an achiral spacer between the two oxazoline units, is the most widely employed ligand (Fig. 1).[11] Upon complexation, a six-membered metal chelate is formed. The chiral substituents on the oxazoline ring are in proximity to the metal centre and, therefore, they directly influence the stereochemical outcome of the enantioselective reaction.

As part of our ongoing interest towards the development of enantioselective catalysts,[8,12] we developed a new class of oxazoline ligands **2**–**6** with a *trans*-(2*R*,3*R*)-diphenylcyclopropane backbone.[13] We have synthesized a ligand bearing only backbone chirality and four ligands with an additional stereogenic centre on the oxazoline moiety. These newly synthesized ligands were tested and compared in palladium(0)-catalysed enantioselective allylic alkylations, copper(I)-catalysed enantioselective cyclopropanations and aziridinations.

2. Results and discussions

2.1. Synthesis of C_2-symmetric bisoxazolines

Several methods have been developed in order to synthesize oxazolines. However, the most widely used method is the reaction of diacid derivatives with chiral amino alcohols followed by cyclization. The synthetic route towards enantiomerically pure bisoxazolines with a *trans*-(2*R*,3*R*)-diphenylcyclopropane backbone started with acid ester **7** (Scheme 1). The latter was synthesized according to a literature procedure starting from *trans*-1,2-diphenylethene.[13–15] Acid ester **7** was first converted through saponification into the corresponding diacid **8** and then into the bis(acid chloride) by treatment of **2** with oxalyl chloride. Without further purification, this bis(acid chloride) was used in the next step. Within 1 h, with 2 equiv of amino alcohol in the presence of triethylamine, the bis(acid chloride) was converted smoothly into the corresponding bishydroxyamides **9**–**13**.[16] The alcohols were further transformed into good leaving groups by treatment with mesylchloride. Subsequent cyclization in an aqueous methanolic solution of sodium hydroxide gave the desired bisoxazolines **2**–**6** in good yields (70–80%).

According to this general procedure, various bisoxazoline ligands could be easily synthesized. In order to investigate the effi-

* Corresponding author. Tel.: +32 9 264 44 80; fax: +32 9 264 49 98.
E-mail address: Johan.Vandereycken@UGent.be (J. Van der Eycken).

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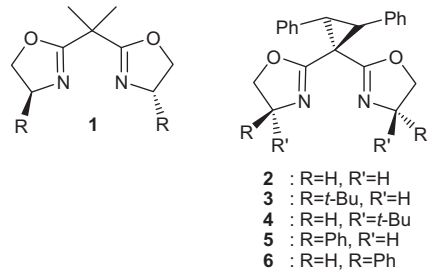
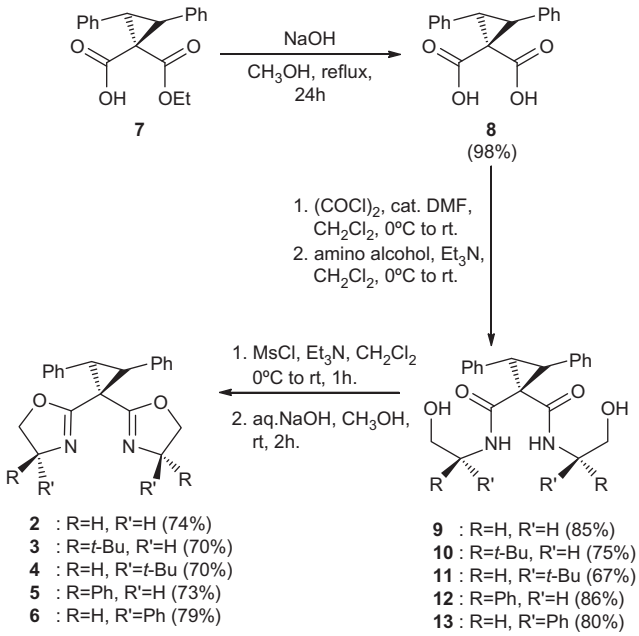


Figure 1. Bisoxazoline ligands.



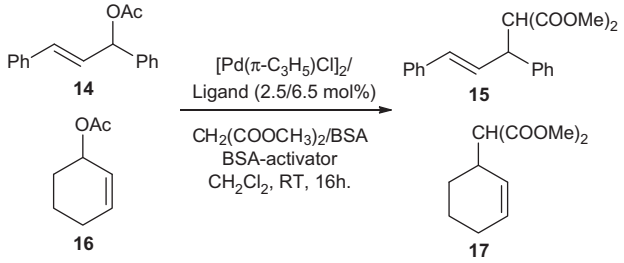
Scheme 1. Synthesis of bisoxazoline ligands **2**–**6**.

ciency of our new backbone, we synthesized a bisoxazoline ligand **2** containing no extra stereogenic centre on the oxazoline moiety (Scheme 1). We synthesized a further four more bisoxazoline ligands: two *tert*-butyl-substituted bisoxazolines **3** and **4** derived from (*S*)- and (*R*)-*tert*-leucinol, respectively, and two phenyl-substituted bisoxazolines **5** and **6** derived from (*S*)- and (*R*)-phenylglycinol, respectively.

2.2. Application in asymmetric catalytic reactions

The palladium(0)-catalysed asymmetric allylic alkylation was chosen as the first catalytic test reaction in order to determine the efficiency of the new bisoxazoline ligands. This reaction is one of the most versatile methods for the formation of carbon–carbon bonds.[17] We focused our attention on the allylic substitution of 1,3-diphenyl-2-propenyl acetate **14** with dimethylmalonate (DMM), which is regarded as a standard test substrate for evaluating enantioselective catalysts (Table 1). The nucleophile was generated from DMM (3 equiv) in the presence of *N*-*O*-bis(trimethylsilyl)acetamide (BSA) (3 equiv) and 0.1 mol % BSA activator. With bisoxazoline ligand **2**, which contains no stereogenic centre on the oxazoline moiety, we obtained a moderate conversion and a low enantioselectivity (Table 1, entry 1). When we used KOAc as a BSA activator, a slightly higher conversion was obtained, however, the enantioselectivity decreased (Table 1, entry 2). An increase in the reaction temperature resulted in a further decrease of the

Table 1
Pd(0)-catalysed asymmetric allylic alkylation of **14** and **16** with dimethylmalonate using bisoxazoline ligands **2**–**6**



Entry	Substrate	Ligand	BSA activator	Yield[a] (%)	ee[b,c] (%)
1	**14**	**2**	LiOAc	53	27 (*S*)
2	**14**	**2**	KOAc	62	21 (*S*)
3[d]	**14**	**2**	KOAc	65	17 (*S*)
4	**14**	**3**	LiOAc	nd	—
5	**14**	**4**	LiOAc	nd	—
6	**14**	**5**	LiOAc	60	97 (*S*)
7	**14**	**6**	LiOAc	90	96 (*R*)
8	**16**	**2**	LiOAc	9	67[e] (*R*)
9	**16**	**3**	LiOAc	9	38[e] (*R*)
10	**16**	**4**	LiOAc	4	48[e] (*S*)
11	**16**	**5**	LiOAc	4	82[e] (*R*)
12	**16**	**6**	LiOAc	3	92[e] (*S*)

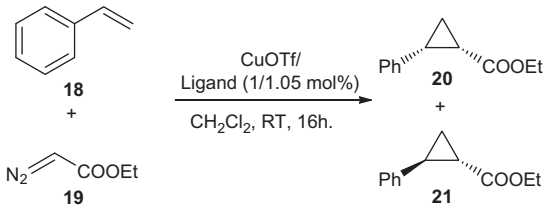
[a] Isolated yield.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralpak AD-H).
[c] Absolute configuration was assigned by the sign of the specific rotation.
[d] Reaction temperature = 50 °C.
[e] Determined by GC analysis with a chiral stationary phase column (Supelco β-Dex).

enantioselectivity (Table 1, entry 3). We observed no conversion at all when we used *tert*-butyl-substituted bisoxazolines **3** and **4** as ligands (Table 1, entries 4 and 5). In sharp contrast, excellent enantioselectivities were obtained with phenyl-substituted bisoxazolines **5** and **6** (Table 1, entries 6 and 7). The best result was obtained with the ligand **6** derived from (*R*)-phenylglycinol: a good yield (90% yield) was combined with an excellent enantioselectivity (96% ee). It is immediately clear that the enantioselectivity is determined by the stereogenic centre on the oxazoline moiety. This is unsurprising, since these chiral substituents are in the immediate vicinity of the metal centre and will therefore direct the stereochemical outcome of the reaction.

Next, we investigated the performance of these bisoxazoline ligands in the allylic alkylation of a cyclic substrate **16**. Although highly selective catalysts have been developed for these cyclic substrates, for example, Trost's ligand, they generally exhibit low enantiocontrol in more hindered substrates, such as substrate **14**. Ligands with a broad substrate scope are very rare.[8c,18] When we performed the reaction with our bisoxazoline ligands, we observed in all cases low conversions (Table 1, entries 8–12). Again, the highest enantioselectivities were obtained with our phenyl-substituted ligands (Table 1, entries 11 and 12).

The bisoxazoline ligands were further tested in the Cu(I)-catalysed enantioselective cyclopropanations of olefins. The enantioselective cyclopropanation of styrene **18** with ethyl diazoacetate **19** is considered as another benchmark reaction to determine the efficiency of the newly developed ligands.[11,19] In order to prevent the formation of diethylmalonate, we slowly added a solution of ethyldiazoacetate **19** over 5 h with a syringe pump and added styrene in excess. Again, with ligand **2**, which lacks a stereogenic centre on the oxazoline, poor enantioselectivity was observed (Table 2, entry 1). In contrast with the asymmetric allylic alkylation, the best

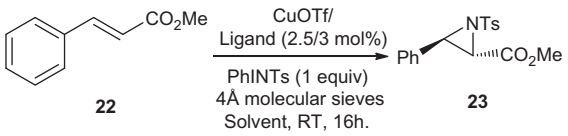
Table 2
Cu(I)-catalysed enantioselective cyclopropanation of styrene **18** using bisoxazoline ligands **2**–**6**



Entry	Ligand	Yield[a] (%)	*cis*/*trans* ratio[b]	ee *cis* **20**[b,c] (%)	ee *trans* **21**[b,c] (%)
1	**2**	67	32/68	<5 (1*S*,2*R*)	<5 (1*S*,2*S*)
2	**3**	72	35/65	83 (1*R*,2*S*)	85 (1*R*,2*R*)
3	**4**	69	22/78	73 (1*S*,2*R*)	89 (1*S*,2*S*)
4	**5**	68	33/67	26 (1*R*,2*S*)	35 (1*R*,2*R*)
5	**6**	76	33/67	20 (1*S*,2*R*)	26 (1*S*,2*S*)

[a] Isolated yield.
[b] The *cis*/*trans* ratio and the enantioselectivity were determined by GC analysis with a chiral stationary phase column (CycloSil-B).
[c] Absolute configuration was assigned by the sign of the specific rotation.

Table 3
Cu(I)-catalysed enantioselective aziridination of methyl cinnamate (**22**) using bisoxazoline ligands **2**–**6**



Entry	Ligand	Solvent	Yield[a] (%)	ee[b,c] (%)
1	**2**	CH_3CN	14	<5 (nd)
2	**2**	C_6H_6	24	19 (2*R*,3*S*)
3	**2**	CH_2Cl_2	4	15 (2*R*,3*S*)
4	**3**	C_6H_6	4	<5 (nd)
5	**3**	CH_3CN	14	6 (2*R*,3*S*)
6	**4**	C_6H_6	13	<5 (nd)
7	**4**	CH_3CN	23	<5 (nd)
8	**5**	C_6H_6	28	85 (2*R*,3*S*)
9	**5**	CH_3CN	23	32 (2*R*,3*S*)
10	**6**	C_6H_6	25	90 (2*S*,3*R*)
11	**6**	CH_3CN	18	29 (2*S*,3*R*)

[a] Isolated yield.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H).
[c] Absolute configuration was assigned by the sign of the specific rotation.

results were obtained with the *tert*-butyl-substituted bisoxazolines **3** and **4** (Table 2, entries 2 and 3). A very good enantioselectivity and good diastereoselectivity were achieved with ligand **4** (Table 2, entry 3). Again we observed that the induced selectivity was strongly dependent on the stereogenic centre present on the oxazoline moiety (Table 2, entries 2–5).

Finally, we selected the Cu(I)-catalysed enantioselective aziridination to test our bisoxazoline ligands. Aziridines are very versatile building blocks in organic chemistry as they exhibit a similar reactivity pattern to epoxides.[20] In sharp contrast with these epoxides, the methods for asymmetric aziridine formation are rare.[21] This is due to the fact that the discovery of useful methods for catalytic asymmetric aziridination has proven to be extremely difficult. An interesting methodology to obtain chiral aziridines is the Cu(I)-catalysed asymmetric aziridination of alkenes.[22]

The catalytic asymmetric aziridination of methyl cinnamate was carried out with (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhINTs) as a nitrene precursor at room temperature. With ligand **2**, we obtained poor results in acetonitrile (Table 3, entry 1). Changing the solvent to benzene or dichloromethane resulted in higher enantioselectivities (Table 3, entries 2 and 3). However, the yields remained unacceptable. In general, poor results were also obtained with the *tert*-butyl-substituted bisoxazolines **3** and **4** (Table 3, entries 4–7). The best results were again obtained with the phenyl-substituted bisoxazolines (Table 3, entries 8–11). Interestingly, a very pronounced solvent effect was observed: in apolar benzene, significantly higher enantioselectivities (up to 90% ee) were obtained in comparison to polar acetonitrile. Although the enantioselectivities are noteworthy, the conversions were very poor.

3. Conclusion

In summary, we have developed a new class of bisoxazolines with a *trans*-(2*R*,3*R*)-diphenylcyclopropane backbone. Their effectiveness was illustrated in palladium(0)-catalysed asymmetric allylic alkylations, copper(I)-catalysed cyclopropanations and copper(I)-catalysed aziridinations. We demonstrated that the presence of a stereogenic centre on the oxazoline moiety is mandatory in order to obtain acceptable enantioselectivities. In addition, our results clearly show that the nature of the substituent on the chiral oxazoline ring is crucial. For asymmetric allylic alkylations (up to 97% ee) and aziridinations (up to 90% ee), the best results were obtained with the phenyl-substituted bisoxazolines. In contrast, *tert*-butyl-substituted bisoxazolines appeared to be the ligands of choice for the cyclopropanations (up to 89% ee). Moreover, we observed that the induced selectivity is strongly dependent on the absolute chirality of the stereogenic centre on the oxazoline moiety.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere in dry solvents under anhydrous conditions, unless otherwise stated. All reagents were purchased and used without purification, unless otherwise noted. Analytical TLC was performed using Macherey-Nagel SIL G-25 UV_{254} plates. Flash chromatography was carried out with Rocc silica gel (0.040–0.063 mm). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or a Bruker DRX 500 spectrometer as indicated, with chemical shifts reported in ppm relative to TMS, using the residual solvent signal as a standard. ^{13}C NMR spectra were recorded using the attached proton test. IR-spectra were recorded on a Perkin–Elmer SPECTRUM-1000 FT-IR spectrometer with a Pike Miracle Horizontal Attenuated Total Reflectance (HATR) module. EI Mass spectra were recorded with a Hewlett–Packard 5988A mass spectrometer. LC–MS analysis was performed on an Agilent 1100 series HPLC with quaternary pump, DAD and single quadrupole MS detector type VL with an API-ES source, using a Phenomenex Luna C18(2) column (250 × 4.6 mm, particle size 5 μm). Analytical chiral HPLC separations were performed on an Agilent 1100 series HPLC system with DAD detection. Exact molecular masses were measured on a quadrupole/orthogonal-acceleration time-of-flight (Q/oaTOF) tandem mass spectrometer (qTof 2, Micromass, Manchester, UK) equipped with a standard electrospray ionization (ESI) interface. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Melting points were measured with a Kofler melting point apparatus.

4.2. Synthesis of (2*R*,3*R*)-diacid 8

To a solution of acid ester **7** (1.0 g, 3.22 mmol) in CH_3OH (11 mL) was added aqueous NaOH (2 M, 11 mL). The mixture was

refluxed for 24 h after which, methanol was removed in vacuo. The residue was cooled to 0 °C and acidified with aqueous HCl (6 M). The acidified mixture was extracted with ether (3 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered off and concentrated to give **8**, 0.890 g (98%), as a colourless oil. The crude (2*R*,3*R*)-diacid was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (s, 2H), 7.20–7.40 (m, 10H), 9.50 (br s, 2H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 38.3 (CH), 43.1 (C), 127.9 (CH), 128.5 (CH), 128.9 (CH), 133.6 (C), 171.5 (C) ppm. IR (HATR): 3029, 2549, 1978, 1685, 1497, 1417, 1296, 1150, 778, 732, 693 cm^{-1}. ES-MS: 281 $[M-H]^-$. $[\alpha]_D^{20} = +56.5$ (*c* 1.02, $CHCl_3$). HRMS (EI) calcd for $C_{17}H_{14}O_4$: 282.0892; found 282.0898.

4.3. A typical procedure for the preparation of the bishydroxyamides 9–13

Oxalyl chloride (0.652 g, 5.13 mmol) was added dropwise to a solution of (2*R*,3*R*)-diacid **8** (0.5 g, 1.77 mmol) and DMF (30 μL) in CH_2Cl_2 (5 mL) over 20 min at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature and was stirred for another 5 h. The volatiles were removed under reduced pressure to afford the crude acid chloride. The acid chloride was dissolved in CH_2Cl_2 and then added dropwise to a mixture of the corresponding amino ethanol (3.45 mmol) and Et_3N (0.875 g, 8.65 mmol) in CH_2Cl_2 (5 mL) over 40 min. After 1 h, the resulting suspension was diluted with CH_2Cl_2 and washed with HCl (1 M, 20 mL); saturated with $NaHCO_3$ (20 mL) and brine (20 mL). The combined organic phases were dried over Na_2SO_4, filtered off and concentrated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 90/10) to give the corresponding bishydroxyamide **9–13**.

4.3.1. (2*R*,3*R*)-1,1-Bis-[(2′-hydroxyethyl)aminocarbonyl]-2,3-diphenylcyclopropane 9

The reaction was performed on (2*R*,3*R*)-diacid **8** (0.5 g, 1.77 mmol) according to the typical procedure, using amino ethanol (0.211 g, 3.45 mmol). Purification by flash chromatography over silica gel (CH_2Cl_2/MeOH, 90/10) resulted in pure bishydroxyamide **9** as a pale yellow solid, 0.542 g (85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15 (m, 4H), 3.25 (m, 2H), 3.40 (m, 2H), 3.72 (s, 2H), 6.70 (t, *J* = 5.8 Hz, 2H), 7.25–7.40 (m, 10H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 33.0 (CH), 42.6 (CH_2), 48.9 (C), 61.4 (CH_2), 127.3 (CH), 128.3 (CH), 128.4 (CH), 135.4 (C), 167.3 (C) ppm. IR (HATR): 3277, 3064, 2940, 1630, 1540, 1493, 1304, 1055, 1030, 744, 695 cm^{-1}. ES-MS: 369 $[M+H]^+$. $[\alpha]_D^{20} = +84.8$ (*c* 1.0, EtOH). Mp 115–117 °C. HRMS (EI) calcd for $C_{21}H_{24}N_2O_4$: 368.1736; found 368.1744.

4.3.2. (2*R*,3*R*)-1,1-Bis-[*N*-(1′*S*)-(1′-*tert*-butyl-2′-hydroxyethyl) aminocarbonyl]-2,3-diphenylcyclopropane 10

The reaction was performed on (2*R*,3*R*)-diacid **8** (0.3 g, 1.06 mmol) according to the typical procedure, using (*S*)-*tert*-leucinol (0.230 g, 1.95 mmol). Purification by flash chromatography over silica gel (hexane/EtOAc, 30/70) resulted in pure bishydroxyamide **10** as a white solid, 0.380 g (75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.45 (s, 18H), 3.30 (m, 2H), 3.60–3.75 (m, 4H), 3.80 (s, 2H), 6.12 (d, *J* = 9.6 Hz, 2H), 7.25 (m, 2H), 7.32 (m, 4H), 7.45 (m, 4H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 26.4 (CH_3), 32.7 (C), 33.0 (CH), 50.4 (C), 60.0 (CH), 62.3 (CH_2), 127.2 (CH), 128.5 (CH), 128.6 (CH), 135.3 (C), 167.5 (C) ppm. IR (HATR): 3379, 3322, 2950, 2356, 2335, 1637, 1539, 1498, 1364, 1294, 1046, 1023, 998, 742, 694 cm^{-1}. ES-MS: 481 $[M+H]^+$. $[\alpha]_D^{20} = +43.5$ (*c* 1.0, $CHCl_3$). Mp 112–114 °C. HRMS (EI) calcd for $C_{29}H_{40}N_2O_4$: 480.2988; found 480.3007.

4.3.3. (2*R*,3*R*)-1,1-Bis-[*N*-(1′*R*)-(1′-*tert*-butyl-2′-hydroxyethyl) aminocarbonyl]-2,3-diphenylcyclopropane 11

The reaction was performed on (2*R*,3*R*)-diacid **8** (0.3 g, 1.06 mmol) according to the typical procedure, using (*R*)-*tert*-leucinol (0.230 g, 1.95 mmol). Purification by flash chromatography over silica gel (hexane/EtOAc, 30/70) resulted in pure bishydroxyamide **11** as a white solid, 0.340 g (67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.70 (s, 18H), 2.82–2.90 (m, 2H), 3.26–3.35 (m, 2H), 3.45–3.55 (m, 2H), 3.72 (s, 2H), 6.30 (d, *J* = 9.1 Hz, 2H), 7.20–7.30 (m, 2H), 7.35–7.52 (m, 8H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 26.7 (CH_3), 32.2 (CH), 33.2 (C), 47.9 (C), 60.4 (CH), 62.8 (CH_2), 127.9 (CH), 128.5 (CH), 129.0 (CH), 135.3 (C), 167.7 (C) ppm. IR (HATR): 3405, 3312, 2956, 2878, 1665, 1638, 1498, 1475, 1366, 1346, 1232, 1050, 979, 739, 698 cm^{-1}. ES-MS: 481 $[M+H]^+$. $[\alpha]_D^{20} = +28.7$ (*c* 1.0, $CHCl_3$). Mp 147–149 °C. HRMS (EI) calcd for $C_{29}H_{40}N_2O_4$: 480.2988; found 480.2991.

4.3.4. (2*R*,3*R*)-1,1-Bis-[*N*-(1′*S*)-(1′-phenyl-2′-hydroxy ethyl)aminocarbonyl]-2,3-diphenylcyclopropane 12

The reaction was performed on (2*R*,3*R*)-diacid **8** (0.3 g, 1.06 mmol) according to the typical procedure, using (*S*)-phenylglycinol (0.265 g, 1.90 mmol). Purification by flash chromatography over silica gel (hexane/EtOAc, 30/70) resulted in pure bishydroxyamide **12** as a white solid, 0.475 g (86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.50 (m, 2H), 3.70 (s, 2H), 3.77 (m, 4H), 4.95 (m, 2H), 6.65 (d, *J* = 7.3 Hz, 4H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.97–7.12 (m, 10H), 7.20 (m, 4H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 33.2 (CH), 49.5 (C), 55.6 (CH), 65.6 (CH_2), 126.4 (CH), 126.7 (CH), 127.2 (CH), 127.4 (CH), 128.2 (CH), 128.4 (CH), 135.1 (C), 137.6 (C), 167.0 (C) ppm. IR (HATR): 3408, 3307, 2958, 2873, 1665, 1635, 1524, 1498, 1475, 1366, 1051, 1031, 743, 700 cm^{-1}. ES-MS: 521 $[M+H]^+$. $[\alpha]_D^{20} = +134.4$ (*c* 1.0, $CHCl_3$). Mp 121–123 °C. HRMS (EI) calcd for $C_{33}H_{32}N_2O_4$: 520.2362; found 520.2377.

4.3.5. (2*R*,3*R*)-1,1-Bis-[*N*-(1′*R*)-(1′-phenyl-2′-hydroxyethyl) aminocarbonyl]-2,3-diphenylcyclopropane 13

The reaction was performed on (2*R*,3*R*)-diacid **8** (0.3 g, 1.06 mmol) according to the typical procedure, using (*R*)-phenylglycinol (0.265 g, 1.90 mmol). Purification by flash chromatography over silica gel (hexane/EtOAc, 30/70) resulted in pure bishydroxyamide **13** as a white solid, 0.440 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30–3.40 (m, 2H), 3.40–3.50 (m, 2H), 3.85 (s, 2H), 4.8 (m, 2H), 6.60 (d, *J* = 7.5 Hz, 2H), 6.95 (m, 4H), 7.10–7.20 (m, 6H), 7.40–7.50 (m, 10H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 32.6 (CH), 48.5 (C), 55.9 (CH), 65.8 (CH_2), 126.5 (CH), 126.5 (CH), 127.7 (CH), 127.7 (CH), 128.5 (CH), 128.8 (CH), 135.2 (C), 138.2 (C), 166.4 (C) ppm. IR (HATR): 3426, 3387, 3276, 3028, 2361, 1625, 1553, 1496, 1449, 1284, 1060, 1028, 977, 745, 695 cm^{-1}. ES-MS: 521 $[M+H]^+$. $[\alpha]_D^{20} = -13.7$ (*c* 1.0, $CHCl_3$). Mp 193–195 °C. HRMS (EI) calcd for $C_{33}H_{32}N_2O_4$: 520.2362; found 520.2352.

4.4. A typical procedure for the preparation of the bisoxazoline ligands 2–6

A mixture of bishydroxyamide **9–13** (0.81 mmol) and Et_3N (0.923 g, 9.12 mmol) in CH_2Cl_2 (10 mL) was stirred at 0 °C. Next, MsCl (0.186 g, 1.62 mmol) was added dropwise over 10 min. The mixture was allowed to warm to room temperature and was stirred for an additional hour. The mixture was washed with water and the organic phases were dried over Na_2SO_4, filtered off and concentrated in vacuo to give the corresponding crude bismesylate as a yellow oil. Next, the crude bismesylate was dissolved in CH_3OH (10 mL) and was treated with aq NaOH (1 M, 2 mL) at room temperature for 2 h. After removal of methanol in vacuo, CH_2Cl_2 was added and washed with water. The organic phases were dried

over Na_2SO_4, filtered off and concentrated in vacuo. The crude product was purified by flash chromatography over silica gel.

4.4.1. (2*R*,3*R*)-1,1-Bis-[oxazolin-2'-yl]-2,3-diphenylcyclopropane 2

The reaction was performed on bishydroxyamide **9** (0.3 g, 0.81 mmol) according to the typical procedure. Purification by flash chromatography over silica gel (CH_2Cl_2/MeOH, 93/7) resulted in pure bisoxazoline **2** as a colourless viscous oil, 0.20 g (74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42–3.55 (m, 2H), 3.70–3.80 (m, 2H), 3.85 (s, 2H), 3.90–4.00 (m, 4H), 7.20–7.30 (m, 6H), 7.35–7.40 (m, 4H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 34.1 (C), 34.4 (CH), 54.0 (CH_2), 67.9 (CH_2), 127.1 (CH), 128.0 (CH), 128.9 (CH), 135.3 (C), 163.4 (C) ppm. IR (HATR): 3311, 3059, 2965, 2900, 1660, 1602, 1497, 1355, 1252, 1213, 1143, 1093, 1069, 991, 927, 761, 749, 714, 695 cm^{-1}. ES-MS: 333 [M+H]$^+$. $[\alpha]_D^{20} = +99$ (*c* 1.0, $CHCl_3$). HRMS (ES) calcd for $C_{21}H_{20}N_2O_2$: 333.1597; found 333.1621.

4.4.2. (2*R*,3*R*)-1,1-Bis-[(4′*S*)-4′-*tert*-butyloxazolin-2′-yl]-2,3-diphenylcyclopropane 3

The reaction was performed on bishydroxyamide **10** (0.350 g, 0.73 mmol) according to the typical procedure. Purification by flash chromatography over silica gel (hexane/EtOAc, 70/30) resulted in pure bisoxazoline **3** as a colourless oil, 0.228 g (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.45 (s, 18H), 3.62–3.70 (m, 4H), 3.75 (s, 2H), 3.85–3.95 (m, 2H), 7.10–7.20 (m, 2H), 7.25–7.30 (m, 4H), 7.40–7.50 (m, 4H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 25. 5 (CH_3), 33.1 (C), 33.2 (C), 34.2 (CH), 69.0 (CH_2), 75.8 (CH), 127.1 (CH), 128.1 (CH), 129.6 (CH), 135.6 (C), 162.6 (C) ppm. IR (HATR): 2951, 2899, 1662, 1604, 1476, 1360, 1338, 1253, 1208, 1144, 1101, 995, 946, 746, 695 cm^{-1}. ES-MS: 445 [M+H]$^+$. $[\alpha]_D^{20} = +19$ (*c* 1.0, $CHCl_3$). HRMS (ES) calcd for $C_{29}H_{36}N_2O_2$: 445.2849; found 445.2866.

4.4.3. (2*R*,3*R*)-1,1-Bis-[(4′*R*)-4′-*tert*-butyloxazolin-2′-yl]-2,3-diphenylcyclopropane 4

The reaction was performed on bishydroxyamide **11** (0.3 g, 0.69 mmol) according to the typical procedure. Purification by flash chromatography over silica gel (hexane/EtOAc, 70/30) resulted in pure bisoxazoline **4** as a colourless oil, 0.215 g (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72 (s, 18H), 3.50 (m, 2H), 3.60–3.67 (m, 2H), 3.7 (s, 2H), 3.72 (m, 2H), 7.10–7.20 (m, 6H), 7.28–7.32 (m, 4H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 25.8 (CH_3), 33.5 (C), 34.0 (CH), 34.6 (C), 68.7 (CH_2), 75.3 (CH), 126.8 (CH), 127.9 (CH), 128.9 (CH), 136.0 (C), 162.0 (C) ppm. IR (HATR): 2956, 2900, 1666, 1496, 1477, 1387, 1356, 1250, 1194, 1089, 1020, 986, 767, 696 cm^{-1}. ES-MS: 445 [M+H]$^+$. $[\alpha]_D^{20} = +160.2$ (*c* 1.0, $CHCl_3$). HRMS (ES) calcd for $C_{29}H_{36}N_2O_2$: 445.2849; found 445.2844.

4.4.4. (2*R*,3*R*)-1,1-Bis-[(4′*S*)-4′-phenyloxazolin-2′-yl]-2,3-diphenylcyclopropane 5

The reaction was performed on bishydroxyamide **12** (0.450 g, 0.87 mmol) according to the typical procedure. Purification by flash chromatography over silica gel (hexane/EtOAc, 70/30) resulted in pure bisoxazoline **5** as a colourless oil, 0.305 g (73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (dd (app. t), *J* = 8.5 Hz, 2H), 4.08 (s, 2H), 4.57 (dd, *J* = 8.5 Hz, 10.0 Hz 2H), 5.15 (dd (app. t), *J* = 10.0 Hz, 2H), 6.45 (d, *J* = 7.5 Hz, 4H), 7.10–7.20 (m, 6H), 7.30–7.40 (m, 6H), 7.5–7.58 (m, 4H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 33.4 (C), 34.6 (CH), 69.7 (CH), 75.8 (CH_2), 126.7 (CH), 127.3 (CH), 127.4 (CH), 128.4 (CH), 128.5 (CH), 129.7 (CH), 135.4 (C), 141.5 (C), 164.1 (C) ppm. IR (HATR): 3035, 2910, 1659, 1602, 1494, 1448, 1352, 1312, 1143, 1101, 990, 933, 757, 695 cm^{-1}. ES-MS: 485 [M+H]$^+$. $[\alpha]_D^{20} = +18.2$ (*c* 1.0, $CHCl_3$). HRMS (ES) calcd for $C_{33}H_{28}N_2O_2$: 485.2223; found 485.2253.

4.4.5. (2*R*,3*R*)-1,1-Bis-[(4′*R*)-4′-phenyloxazolin-2′-yl]-2,3-diphenylcyclopropane 6

The reaction was performed on bishydroxyamide **13** (0.430 g, 0.83 mmol) according to the typical procedure. Purification by flash chromatography over silica gel (hexane/EtOAc, 70/30) resulted in pure bisoxazoline **6** as a colourless oil, 0.316 g (79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (dd (app. t), *J* = 8.5 Hz, 2H), 4.05 (s, 2H), 4.35 (dd, *J* = 8.5 Hz, 10.0 Hz, 2H), 5.92 (dd (app. t), *J* = 10.0 Hz, 2H), 7.05 (m, 4H), 7.20–7.35 (m, 12H), 7.50 (m, 4H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 34.3 (CH), 34.5 (C), 69.7 (CH), 74.9 (CH_2), 126.9 (CH), 127.2 (CH), 127.4 (CH), 128.1 (CH), 128.5 (CH), 129.1 (CH), 135.1 (C), 141.7 (C), 163.6 (C) ppm. IR (HATR): 3028, 2900, 1657, 1603, 1495, 1450, 1352, 1271, 1151, 1093, 989, 933, 758, 695 cm^{-1}. ES-MS: 485 [M+H]$^+$. $[\alpha]_D^{20} = +193.6$ (*c* 1.0, $CHCl_3$). HRMS (ES) calcd for $C_{33}H_{28}N_2O_2$: 485.2223; found 485.2228.

4.5. General procedure for the palladium(0)-catalysed asymmetric allylic alkylation

Bisoxazoline ligand **2**–**6** (0.05 mmol) and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.02 mmol) were dissolved in degassed CH_2Cl_2 under an argon atmosphere using Schlenk techniques. The reaction mixture was stirred for 1 h at 50 °C and cooled to room temperature. Then *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **13** (1 mmol) in CH_2Cl_2 was added and stirred at room temperature for 30 min. Finally, a solution of BSA (3 mmol), LiOAc (0.1 mmol) and dimethylmalonate (3 mmol) was added to the mixture. The reaction mixture was stirred for 16 h at room temperature. Next, diethylether was added, washed with saturated NH_4Cl, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc, 90/10) to afford the target compound.

All adducts were fully characterized by comparison of their spectroscopic data with those reported in the literature. The absolute configurations were assigned via the correlation of their specific rotation with the literature values.[23]

For **15**: The enantiomeric excess was determined by chiral HPLC analysis: Chiralpak AD-H column (250 × 4.6 mm, particle size 10 μm), solvent: *n*-hexane/EtOH (70/30), flow rate = 1 mL/min, *T* = 35 °C, retention times: 9.2 min for (*S*)-(−)-**15** and 13.9 min for (*R*)-(+)-**15**.

For **17**: The enantiomeric excess was determined by chiral GC analysis: Supelco β-Dex 120 (30 m × 0.25 mm × 0.25 μm); temperature programme: 120 °C (isothermic), retention times: 36.7 min for (*S*)-(−)-**17** and 37.2 min for (*R*)-(+)-**17**.

4.6. General procedure for the asymmetric cyclopropanation

A suspension of $CuOTf{\cdot}1/2C_6H_6$ (0.01 mmol) and bisoxazoline ligand **2**–**6** (0.012 mmol) in CH_2Cl_2 was stirred under argon atmosphere at room temperature. After 1 h, styrene (7.5 mmol) was added to the resulting green solution. Next, ethyl diazoacetate (1 mmol) was slowly added to the reaction via a syringe pump over 5 h. The reaction mixture was stirred at room temperature overnight. The excess styrene and CH_2Cl_2 were removed under reduced pressure and the crude product was purified by flash chromatography (pentane/EtOAc, 96/4) to afford the cyclopropane esters.

All adducts were fully characterized by comparison of their spectroscopic data with those reported in the literature. The absolute configurations were assigned via correlation of their specific rotation with the literature values.[11]

For **20** and **21**: The enantiomeric excess was determined by chiral GC analysis: CycloSil-B (30 m × 0.25 mm × 0.25 μm); temperature programme: 50 °C for 3 min. increasing to 240 °C (5 °C/min) and 240 °C for 3 min, retention times: 26.6 min for (1*S*,2*R*)-**20**, 26.88 min for (1*R*,2*S*)-**20,** 27.93 min for (1*R*,2*R*)-**21,** 29.99 min for (1*S*,2*S*)-**21**.

4.7. General procedure for the asymmetric aziridination

Bisoxazoline ligand **2**–**6** (0.150 mmol) and CuOTf·1/2C_6H_6 (0.125 mmol) were dissolved in acetonitrile or benzene (1 mL) (Table 3) and the mixture was stirred for 1 h at room temperature. To this reaction were added methylcinnamate (25 mmol) and activated 4Å molecular sieves. Next, PhI = NTs (5 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The crude product was purified by flash chromatography over silica gel (hexane/EtOAc, 90/10).

The adduct **23** was fully characterized by comparison of its spectral data with those reported in the literature. The absolute configuration was assigned a correlation of its specific rotation with the literature values.[22a]

For **23**: The enantiomeric excess was determined by chiral HPLC analysis: Chiralcel OD-H column (250 × 4.6 mm, particle size 10 μm), solvent: *n*-hexane/EtOH (90/10), flow rate = 1 mL/min, T = 35 °C, retention times: 10.7 min for (2*R*,3*S*)-**23** and 16.4 min for (2*S*,3*R*)-**23**.

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