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Asymmetric synthesis of chiral bisoxazolines and their use as ligands in metal catalysis

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Dedicated to Professor Jack Halpern on the occasion of his 80th birthday

Abstract—Novel C_2- and C_1-symmetric chiral bisoxazolines with a cyclic backbone have been synthesized in an asymmetric manner starting from *meso* anhydrides. All synthetic steps are easy to perform and lead to the desired products in good overall yields. Preliminary investigations revealed the applicability of these new compounds as ligands in transfer hydrogenations and various metal-catalyzed enantioselective C–C-bond forming reactions such as cyclopropanations and Diels–Alder reactions.

1. Introduction

Over recent years, C_2-symmetric bisoxazolines have proved to be efficient ligands in a large variety of asymmetric transformations, and several general methods are now available for their synthesis.[1] Due to their great potential, which was demonstrated in the initial applications, much effort has been devoted to the modification of the bisoxazoline framework in order to obtain superior ligands. The conformationally constrained metal chelate and the presence of stereocenters close to the nitrogen donor atoms assure a well ordered chiral environment at the catalytic site. Generally, the chirality in these ligands is derived from the optically active β-amino alcohols employed for the oxazoline ring formation. Since a large variety of enantiomerically pure amino alcohols is easily accessible either by simple reduction of the corresponding α-amino acids, or by means of asymmetric synthesis employing chiral auxiliaries, ligand optimization with respect to variation of the oxazoline groups has encountered no problems so far. The size of the chelate has also proven to be important since it controls the orientation of the substituents around the metal center. Beside this, the number of possible transition states in a particular reaction is minimized by the presence of a C_2-symmetry axis in the chiral ligand. Among all known C_2-symmetric bisoxazolines, the most widely used ones are those forming five- and six-membered metal chelates. In contrast, the development and application of seven-membered chelate systems is still limited. Recently, a new class of chiral 1,4-bisoxazolines with a rigid, cyclic 1,3-dioxolane backbone was introduced and optimized by Andersson for the asymmetric copper-catalyzed cyclopropanation of olefins.[2] Two sets of diastereomeric ligands **1** and **2** were readily available from L-amino acids and either L- or D-tartaric acid. The effect of both the oxazolinyl groups and the substituents on the dioxolane ring on the diastereo- and enantioselectivity of the reaction has been carefully investigated. In the same context, Knight carried out a direct comparison of the level and sense of asymmetric induction in the cyclopropanation and aziridination of styrene.[3] Independently, Ikeda has designed such ligands for the rhodium(I)-catalyzed hydrosilylation of acetophenone.[4] More recently, similar tartrate-based ligands have successfully been applied in the mercuriocyclization of γ-hydroxy-*cis*-alkenes, leading to 2-monosubstituted tetrahydrofurans in up to 95% ee.[5] C_2-symmetric bisoxazolines bearing a bicyclic backbone have been developed and introduced by Takacs for the room temperature enantioselective Diels–Alder reaction.[6] For this purpose, enantiomerically pure (2*S*,3*S*)-bicyclo[2.2.1]hept-5-ene-2-*endo*-3-*exo*-dicarboxylic acid was synthesized by saponification of the diester obtained in the Diels–Alder reaction between cyclopentadiene and L-menthol-derived dimenthyl fumarate.[7] Coupling of the diacid with (*S*)-phenylglycinol and subsequent cyclization afforded the 1,4-box ligand **3** containing all

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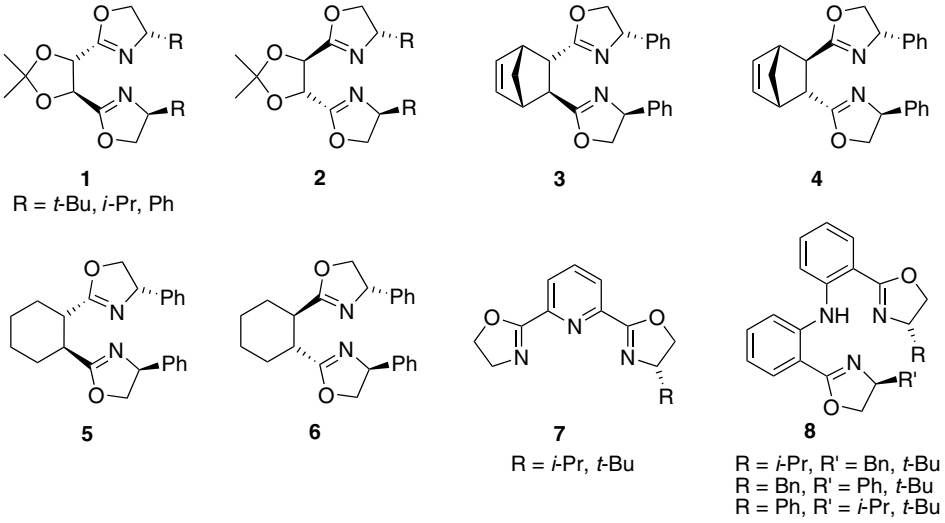
four stereogenic centers of (*S*) absolute configuration. Since the (2*R*,3*R*)-diacid is also available in enantiomerically pure form using the same approach, coupling with (*S*)-phenylglycinol led to a second, diastereomeric ligand **4**. In a similar fashion, chiral box ligands **5** and **6**, based on a *trans*-1,2-cyclohexane skeleton were developed and evaluated together with a series of common ligands in the palladium(II) asymmetric cyclization–carbonylation of 2-propargyl-1,3-dione.[8]

Surprisingly, although the usefulness of C_2-symmetric bisoxazoline ligands is well acknowledged in the literature, the synthesis and application of C_1-symmetric bisoxazolines has not yet been the subject of intensive investigations. Early work from Nishiyama describes the synthesis of an asymmetric bisoxazoline ligand by a stepwise introduction of two different amino alcohols on an achiral backbone.[9] The first coupling step in the sequence made use of dimethyl pyridine-2,6-dicarboxylate and 2-aminoethanol, leading to the corresponding achiral monoamide methyl ester. A chiral amino alcohol was employed in the second step, to give after cyclization, the so-called 'single chiral' pybox type ligand **7**. The resulting ligands were evaluated in the ruthenium-catalyzed cyclopropanation of styrene with various alkyl diazoacetate and enantioselectivities with up to 94% ee were obtained for the *trans* cyclopropane. In 2002, Guiry described the synthesis of a new class of tridentate bisoxazolines **8** by a four-step convergent synthesis, employing a Hartwig–Buchwald type Pd-catalyzed aryl amination as a key step.[10]

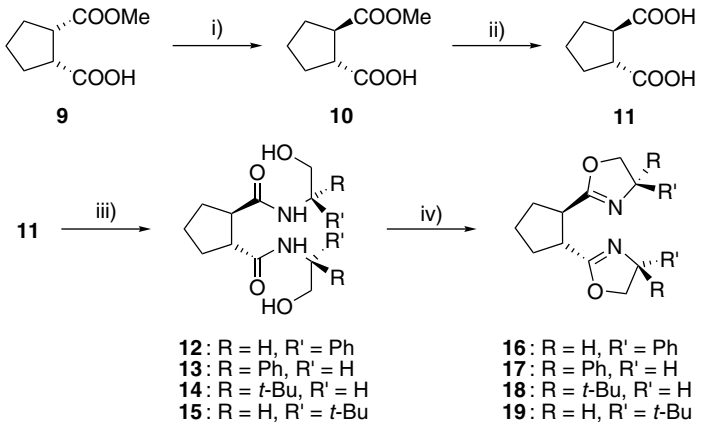


Recently, we described a simple and highly selective organocatalytic desymmetrization methodology, which offers easy access to enantiomerically enriched *cis*-1,2-dicarboxylic methyl- and benzylmonoesters.[11] The synthetic applicability of the method has already been demonstrated by the preparation of optically active β-amino acids,[11c,12] γ-amino alcohols[13] and vicinal diamines.[14] As an extension of our work in this field we present herein a general method for the synthesis of novel 1,4-box ligands with a rigid, cyclic backbone. While designing these compounds, we had in mind several structural features, which should make them effective in metal-catalyzed reactions. As emphasized earlier by Ikeda,[4] the presence of stereogenic centers on the backbone, in addition to those on the oxazoline rings, introduces an extra element of complexity in the ligand structure and special effects could arise when such ligands are employed in asymmetric catalysis. Since both enantiomers of the diacid are readily available from the desymmetrization process, the stereochemistry of the four asymmetric centers is easily adjustable, giving the possibility to investigate and compare their effect on the ligand activity. In addition, the bulkiness of the substituents on the oxazoline rings is adjustable by simply changing the amino alcohol, so the best ligand structure for a particular reaction can be obtained by appropriate selection of stereochemistry and bulkiness.

2. Results and discussion

2.1. C_2-Symmetric bisoxazolines

The synthetic route started with the quinidine-mediated methanolysis of *cis*-cyclopentanedicarboxylic anhydride, which afforded the corresponding methyl hemiester **9** in good yield (95%) and high enantioselectivity (96% ee). Selective epimerization[15] and saponification provided the corresponding *trans* (1*R*,2*R*)-diacid **11** in 78% yield. Next, the Vilsmeier reagent, chloromethylene dimethylammonium chloride, generated in situ from DMF and oxalyl chloride, was employed as an activating reagent. Conversion of the diacid into the corresponding acid dichloride was accomplished within 1 h, the solvent and the excess oxalyl chloride were removed by high vacuum delivering the product, which was used in the next step without further purification. Overnight reaction with 2.2 equiv of the amino alcohol in the presence of triethylamine afforded the expected bishydroxyamide as a white solid, which was insoluble in methylene chloride. All attempts to purify the crude product by an aqueous work up failed. Finally, the bisamide was isolated in enantiomerically and analytically pure form by



Scheme 1. Reagents and conditions: (i) LDA (3.0 equiv), THF, −78 °C, 80%; (ii) NaOH (6.0 equiv), MeOH, 97%; (iii) (a) $(COCl)_2$ (3.0 equiv), DMF (15 mol %), CH_2Cl_2; (b) amino alcohol (2.2 equiv), Et_3N (5 equiv), CH_2Cl_2, 62–70%; (iv) (a) Et_2NSF_3 (2.2 equiv), CH_2Cl_2, −78 °C; (b) K_2CO_3 (3.0 equiv), −78 °C, 80–92%.

simple filtration and washing with methylene chloride. The NMR analysis confirmed the presence of the desired product as a single diastereomer. Activation with diethyl amino sulfur trifluoride[16] in methylene chloride at −78 °C followed by base induced cyclization and purification by column chromatography afforded the corresponding bisoxazoline in high yield.

Following the general reaction Scheme 1, various bisoxazoline derivatives can be easily synthesized starting from (1*R*,2*R*)-diacid **11**. Reaction with (*R*)- and (*S*)-phenylglycinol afforded the products **16** and **17**, respectively, as a pair of two diastereomers. The *tert*-butyl analogs **18** and *ent*-**19** were readily available by reaction of (*S*)-*tert*-leucinol with diacids **11** and *ent*-**11**,[17] respectively.

2.2. C_1-Symmetric bisoxazolines

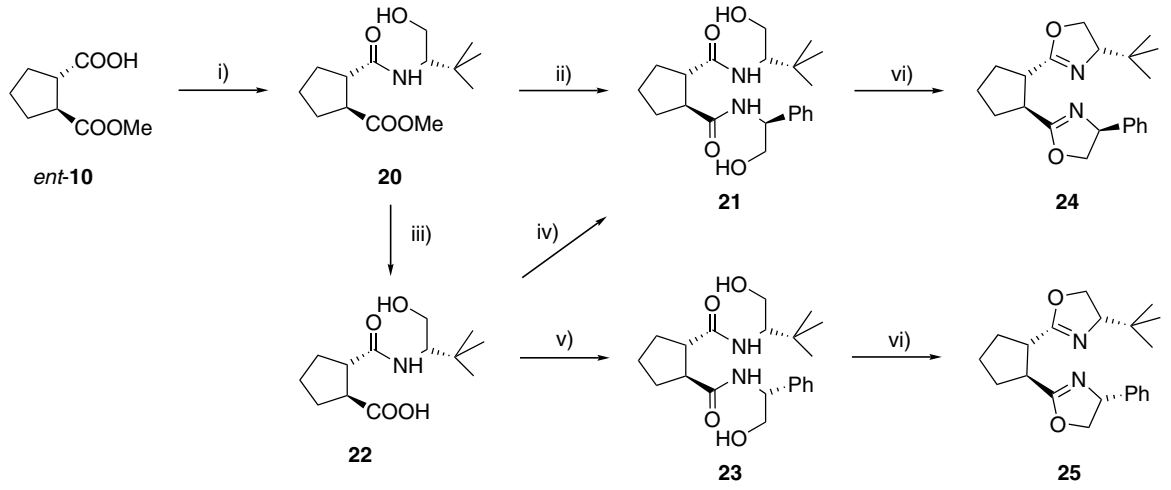
The presence of both a carboxy and a carboxy ester functional group in the same molecule allows a sequential functionalization. We therefore investigated the possibility of a stepwise introduction of two different amino alcohols onto the same chiral backbone. This would permit the synthesis of C_1-symmetric bisoxazolines and one could investigate whether a C_2-symmetric ligand is essential for achieving high levels of diastereo- and enantiocontrol for a specific reaction. In the case of the use of C_1-symmetric ligand the situation is more complex, since the number of possible transition states increases.

In order to validate the design we first synthesized monoamido ester derivative **20** and examined the possibility of introducing a second, different amino alcohol into this molecule. Cyanide catalyzed transamidation[18] afforded the desired mixed bisamide **21** in only 33% yield after chromatographic purification. Due to the low yield, even after extended reaction time, we decided to focus on alternative protocols, which would result in an increase of the reaction yield. Hence, amido ester **20** was converted into the corresponding monoamido acid derivative **22**. The saponification (with NaOH in aqueous methanol) was completed within 4 h (TLC control), and the reaction mixture was acidified and extracted with methylene chloride. Evaporation of the solvent and drying under high vacuum afforded product **22** in 95% yield in analytically pure form.

The presence of a free OH group in **22** excluded the use of activating reagents such as thionyl and oxalyl chloride, and therefore the mixed anhydride formation was chosen for the activation. Treatment with isobutyl chloroformate in THF and reaction of the resulting anhydride with (*S*)-phenylglycinol afforded the desired product in 64% yield after chromatographic purification. In comparison with the first approach, the result was promising but still not satisfactory, and thus applications of alternative coupling reagents were investigated (Scheme 2).

Typical coupling reagents such as DCC and EDCI were excluded due to the potential problems, which could be encountered during the purification process. Highly reactive DCC is the most widely used reagent for amide bond formation and usually gives good yields within short reaction times. However, since the dicyclohexylurea byproduct is almost insoluble in most organic solvents used for coupling reactions and taking into account the above mentioned product insolubility (the bisamide proved to be insoluble in both water and most organic solvents) difficulties in product purification were envisaged. Water-soluble derivatives such as 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), were also eliminated since purification would require an aqueous extraction in order to remove the urea byproduct.

Initially developed as a depressor for the central nervous system,[19] 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) also proved to be an efficient and selective coupling reagent for the formation of peptide bonds.[20] The advantage of EEDQ as coupling reagent is that hydroxy amino acids do not require side-chain protection under the reaction conditions required by the amide bond formation. Furthermore, no racemization occurs



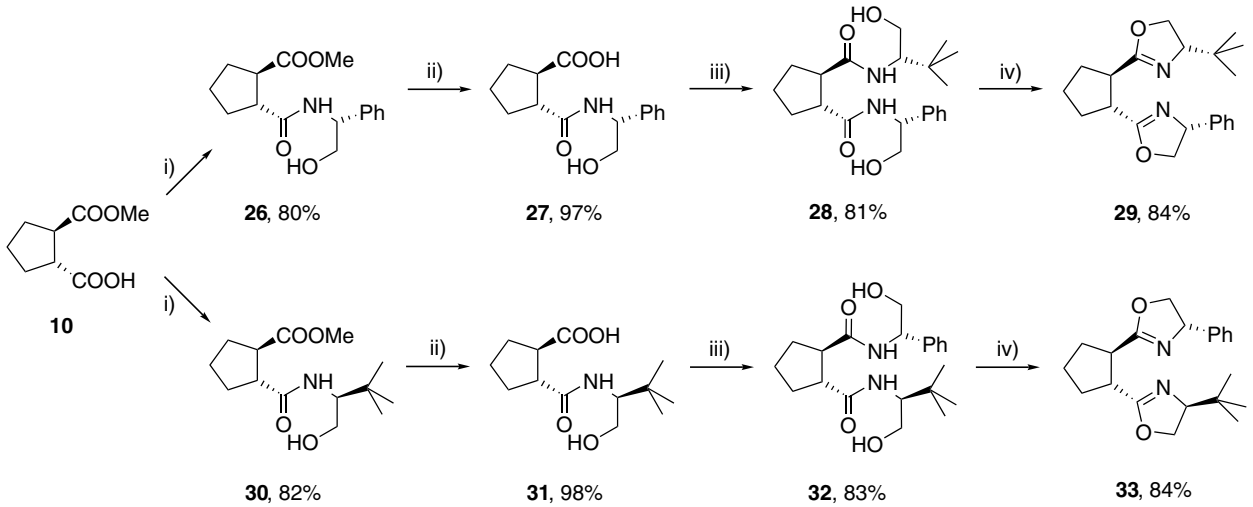
Scheme 2. Reagents and conditions: (i) (a) $(COCl)_2$ (1.5 equiv), DMF (7 mol %), CH_2Cl_2; (b) (*S*)-*tert*-leucinol (1.1 equiv), Et_3N (2.5 equiv), CH_2Cl_2, 87%; (ii) (*S*)-phenylglycinol (1.2 equiv), NaCN (15%), MeOH, 50 °C, 48 h, 33%; (iii) NaOH (3.0 equiv), MeOH, 95%; (iv) method A: (a) ClCOO*i*-Bu (1.0 equiv), THF, NMM (1.0 equiv); (b) (*S*)-phenylglycinol (1.0 equiv), 64%; method B: (*S*)-phenylglycinol (1.0 equiv), EEDQ (1.2 equiv), THF, 0 °C to rt, 5 days, 83%; (v) (*R*)-phenylglycinol (1.0 equiv), EEDQ (1.2 equiv), THF, 0 °C to rt, 5 days, 84%; (vi) (a) Et_2NSF_3 (2.2 equiv), CH_2Cl_2, −78 °C; (b) K_2CO_3 (3.0 equiv), −78 °C.

during this process, and quinoline, ethanol and CO_2 byproducts are all easily removable. The coupling was accomplished efficiently by the one-pot EEDQ procedure,[21] affording mixed bisamide **21** in 83% yield. In the same manner, reaction of **22** with (*R*)-phenylglycinol afforded the corresponding mixed bisamide **23** in 84% yield. Cyclization under the previously described protocol (activation with DAST and subsequent base induced ring closure) afforded the corresponding C_1-symmetric bisoxazolines **24** and **25** in high yields. Since the starting materials are available in both enantiomeric forms, it should be possible to access all four oxazoline combinations of a potential ligand with a cyclopentane backbone. In order to synthesize the two remaining bisoxazolines, the same methodology was successfully applied on the hemiester obtained from the quinidine-mediated methanolysis of *cis*-cyclopentanedicarboxylic anhydride, affording in the end the two desired products **29** and **33** in good overall yields (Scheme 3).

On the one hand, these four mixed bisoxazolines offer the possibility of studying the effect induced by a combination between phenyl as substituent on one oxazoline ring and the bulky *tert*-butyl group on the other one. On the other hand, the effect induced by their different orientations around the metal site is also easy to follow.

2.3. Application in catalysis

The enantioselective Diels–Alder reaction[22] was chosen as the first catalytic test reaction in order to determine the efficiency of the new ligand system. The results of



Scheme 3. Reagents and conditions: (i) (a) $(COCl)_2$ (1.5 equiv), DMF (7 mol %), CH_2Cl_2; (b) amino alcohol (1.1 equiv), Et_3N (2.5 equiv), CH_2Cl_2; (ii) NaOH (3.0 equiv), MeOH; (iii) amino alcohol (1.0 equiv), EEDQ (1.2 equiv), THF, 0 °C to rt, 5 days; (iv) (a) Et_2NSF_3 (2.2 equiv), CH_2Cl_2, −78 °C; (b) K_2CO_3 (3.0 equiv), −78 °C.

the [M(box)]-$(OTf)_2$ catalyzed Diels–Alder reaction between *N*-acryloyl oxazolidinone **34** and cyclopentadiene at room temperature are summarized in Table 1.

The catalysts were prepared by stirring a solution of the corresponding ligand (11 mol %) with the respective metal triflate, $M(OTf)_2$ (10 mol %) in CH_2Cl_2 at room temperature, for 2–3 h. In the case of copper triflate the time was adjusted by checking the solution for the presence of colorless, undissolved triflate salt and by the formation, in all cases, of a clear, green, or blue solution. At this stage the dienophile (0.25 mmol) was added, followed by freshly distilled cyclopentadiene (10 equiv). In all cases the copper complexes exhibited faster reaction rates, affording the products in over 90% yield within 12 h whereas the zinc complexes required longer reaction times, affording products in satisfactory yield in only two cases. Interestingly, the zinc complexes showed a better *endo*:*exo* selectivity compared with the copper analogs. For example, ligand **17** led to a complex in which the two phenyl substituents are pointing toward the metal site and gave the best results in both copper and zinc catalyzed Diels–Alder reaction, namely affording the *endo* product with moderate diastereoselectivity and 71% ee (Table 1, entry 1). A substantial enhancement in the diastereoselectivity (70% vs 54% de) was observed when the zinc complex was employed in the reaction. In contrast, the diastereomeric ligand **16** showed only a low level of asymmetric induction, affording the product with opposite absolute configuration. In the case of **18** and *ent*-**19**, the product was only detected in trace amounts, even if the reaction time was extended to several days. Since $Cu(OTf)_2$ is itself insoluble in methylene chloride and since a clear solution was obtained by mixing it with the ligands **18** and *ent*-**19**, we assume that copper coordinates to both nitrogen atoms, but that the presence of the two bulky *tert*-butyl groups does not offer sufficient space for the dienophile to approach the metal center. This is also the case for the mixed ligand **33** where the two oxazolinyl groups are pointing toward the metal center. If we compare the structure of the best ligand **17** with the one of ligand **33**, it is apparent that the only difference between them is the presence of the bulky *tert*-butyl group instead of the planar phenyl group on one oxazoline ring. This slight modification in the ligand structure causes finally the change from an active complex into an inactive one. In the remaining three mixed ligands, at least one substituent points away from the metal site so that the approach of the dienophile is less hampered compared with **33**. Among them, the metal complex derived from **29** showed the opposite sense of asymmetric induction.

The copper complexes derived from the five ligands, which showed low to moderate activity in the catalyzed Diels–Alder reaction at room temperature were next tested in the reaction at 0 °C. As can be seen in Table 2, the reaction time had to be extended from 12 h to 5 days to achieve good yields. Generally, the reaction at 0 °C afforded the *endo* products with slightly higher enantiomeric excesses.

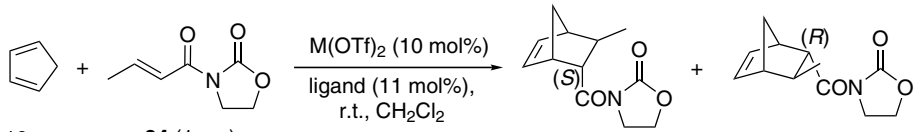
Table 2. Effect of temperature on the Diels–Alder reaction

Entry	Ligand	$Cu(OTf)_2$ (5 days)		
		endo:*exo*[a]	ee[b] (%)	Yield (%)
1	**16**	51:49	23[c]	81
2	**17**	83:17	75	99
3	**24**	60:40	40	81
4	**25**	70:30	16	72
5	**29**	82:18	42[c]	80

[a] The *endo*:*exo* ratios were determined by HPLC analysis and confirmed by NMR spectroscopy.
[b] Determined by HPLC analysis using a chiral stationary phase.
[c] Opposite enantiomer.

Next, the effect of the counterion on the catalyst activity was investigated. Thus, with the bisoxazoline **17** as chiral ligand, various copper sources were tested, and it was

Table 1. Influence of ligand structure on the enantioselective Diels–Alder reaction



Entry	Ligand	$Cu(OTf)_2$ (12 h)			$Zn(OTf)_2$ (36 h)		
		endo:*exo*[a]	ee[b] (%)	Yield (%)	*endo*:*exo*[a]	ee[b] (%)	Yield (%)
1	**16**	52:48	11[c]	93	85:15	38[c]	36
2	**17**	**77:23**	**71**	**96**	**85:15**	**71**	**99**
3	**18**	—	—	—	—	—	—
4	*ent*-**19**	—	—	—	—	—	—
5	**24**	62:38	16	93	86:14	10	33
6	**25**	66:34	23	91	78:22	0	33
7	**29**	73:27	17[c]	98	81:19	55[c]	99
8	**33**	—	—	—	—	—	—

[a] The *endo*:*exo* ratios were determined by HPLC analysis and confirmed by NMR.
[b] Determined by HPLC analysis using a chiral stationary phase.
[c] Opposite enantiomer.

observed that the yield and the *endo*:*exo* ratio remained essentially unaffected whereas the ee of the *endo* product dropped significantly (Table 3).

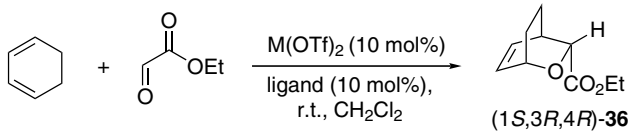
Table 3. Effect of the counterion on the stereoselectivity

Entry	Copper salt	*endo*:*exo*[a]	ee[b] (%)	Yield (%)
1	$Cu(OTf)_2$	77:23	71	96
2	$Cu(SbF_6)_2$	81:19	54	99
3	$Cu(ClO_4)_2$	75:25	46	99

[a] The *endo*:*exo* ratios were determined by HPLC analysis and confirmed by NMR spectroscopy.
[b] Determined by HPLC analysis using a chiral stationary phase.

Subsequently, the related hetero-Diels–Alder (HDA) reaction was investigated,[23] taking 1,3-cyclohexadiene and ethyl glyoxalate as test substrates. The chiral metal catalyst was prepared by mixing equimolar amounts of $Cu(OTf)_2$ (10 mol %) with the respective bisoxazoline ligand (10 mol %) in methylene chloride at room temperature for approximately 2 h. At this stage, freshly distilled ethyl glyoxalate was added, followed by 1,3-cyclohexadiene and the reaction was stirred for 14 h. The results are summarized in Table 4. The [Cu(box)]-$(OTf)_2$ catalyzed reactions of 1,3-cyclohexadiene and ethyl glyoxalate provided the HDA-adduct with high diastereoselectivities (>97% *endo* product) but in moderate yields and with low enantioselectivities (30–49% ee as determined by GC analysis). It should be noted that the complex derived from ligand **29** showed the opposite enantioselectivity.

Table 4. Copper-catalyzed hetero-Diels–Alder reaction



(1*S*,3*R*,4*R*)-**36**

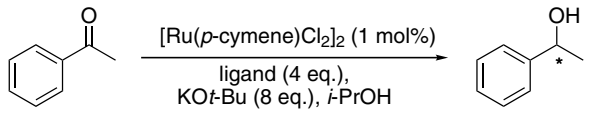
Entry	Ligand	$Cu(OTf)_2$ (14 h)		
		endo:*exo*[a]	ee[a] (%)	Yield (%)
1	**16**	97:3	39	65
2	**17**	97:3	49	68
3	**18**	—	—	—
4	*ent*-**19**	—	—	—
5	**24**	97:3	45	70
6	**25**	98:2	30	50
7	**29**	98:2	37[b]	55
8	**33**	—	—	—

[a] Determined by GC analysis using a chiral stationary phase.
[b] Opposite enantiomer.

The catalytic behavior of the ruthenium complexes derived from the new bisoxazoline ligands was next investigated in the asymmetric transfer hydrogenation of acetophenone.[24] In all cases the catalytic system only gave low enantioselectivities (22–26% ee) (Table 5).

The enantioselective cyclopropanation of olefins is an area of current interest.[25] A major advancement in this field was achieved by Pfaltz, who demonstrated that the Cu(I) complexes derived from C_2-symmetric chiral

Table 5. Ruthenium-catalyzed transfer hydrogenation



Entry	Ligand	$[Ru(p\text{-cymene})Cl_2]_2$ (10 h)	
		ee[a] (%)	Conv. (%)
1	**16**	26 (*R*)	73
2	**17**	24 (*S*)	97
3	**18**	0	26
4	**24**	24 (*S*)	77
5	**25**	22 (*R*)	51
6	**29**	26 (*S*)	90

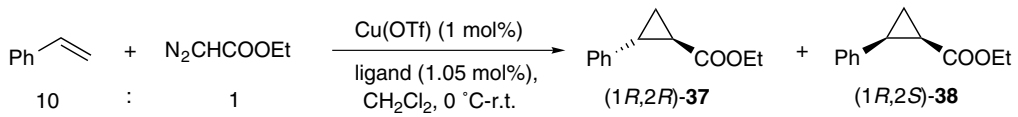
[a] Determined by GC analysis using a chiral stationary phase.

semicorrins were useful catalysts for the enantioselective cyclopropanation of olefins with diazo compounds.[26] Subsequently, copper and ruthenium-box complexes emerged as efficient catalysts for the enantioselective cyclopropanation reaction.[27] Recent reports from Andersson on comparative studies on the effect of the chelate ring size on the ligand activity[2] encouraged us to evaluate the set of bisoxazoline ligands in the intermolecular cyclopropanation reaction.

In a preliminary study, styrene and ethyl diazoacetate were chosen as standard substrates in order to determine the efficiency of the ligand system. The cyclopropanation was carried out in the presence of 1 mol % of CuOTf and 1.05 mol % of chiral ligand in dry methylenechloride. The optimum complexation time was established to be 1 h. Then, the catalyst solution was cooled to 0 °C, styrene was added, followed by slow addition of the ethyl diazoacetate solution (in methylene chloride) over 5 h via syringe pump. The reaction was stirred overnight at room temperature and the results are summarized in Table 6. All four mixed ligands showed low or no asymmetric induction. The two diastereomeric C_2-symmetric ligands bearing phenyl groups on the oxazoline rings exhibited slightly higher levels of asymmetric induction (but still insufficient) compared to the mixed ones, affording the trans products with 36% and 35% ee, respectively.

The *tert*-butyl derivative *ent*-**19** was the most effective ligand, delivering the trans and cis cyclopropanated products with 83% and 87% ee, respectively. Most probably, in this particular case, the bulky *tert*-butyl groups pointing away from the metal center are capable of controlling the olefin approach in an efficient manner, while the planar phenyl groups are not. In situ generation of the active Cu(I) catalyst by reduction of the Cu(II) complex with phenylhydrazine afforded the products with slightly lower enantioselectivities. Addition of the ethyl diazoacetate at room temperature over 5 h also resulted in a decrease in the enantioselectivity. In contrast, diastereomeric ligand **18** afforded products with 10% and 9% ee, respectively. This is, most probably, due to the steric hindrance induced by two bulky oxazolinyl groups pointing in such a way that does not allow the metal to simultaneously coordinate to both nitrogen atoms of the

Table 6. Enantioselective cyclopropanation of styrene



Entry	Ligand	Trans:cis[a]	ee[b] (trans) (%)	ee[c] (cis) (%)	Yield (%)
1	**16**	72:28	36 (1*S*,2*S*)[d]	26 (1*S*,2*R*)	65
2	**17**	72:28	35 (1*R*,2*R*)	8 (1*R*,2*S*)	67
3	**18**	50:50	10 (1*S*,2*S*)	9 (1*S*,2*R*)	70
4	*ent*-**19**	63:37	83 (1*R*,2*R*)	87 (1*R*,2*S*)	72
5	**24**	65:35	21 (1*R*,2*R*)	20 (1*R*,2*S*)	68
6	**25**	63:37	11 (1*S*,2*S*)	8 (1*R*,2*S*)	63
7	**29**	66:34	13 (1*R*,2*R*)	11 (1*R*,2*S*)	60
8	**33**	61:39	0	0	65

[a] The trans:cis ratios were determined by NMR analysis of the crude reaction mixture.
[b] Determined by HPLC analysis using a chiral stationary phase.
[c] Determined by optical rotation.
[d] The absolute configuration was confirmed by the sign of the optical rotation.

oxazoline rings. The reaction is probably catalyzed by free or mono-coordinated Cu species, leading to almost racemic products in good yields. Studies concerning the efficiency of the complex derived from *ent*-**19** in the reaction of different diazoacetate esters with various olefins are currently in progress.

3. Conclusions

In conclusion we have developed an efficient strategy, which allows the synthesis of novel C_2- and C_1-symmetric chiral bisoxazolines with a rigid, cyclic backbone. All the synthetic steps are easy to perform giving the desired products in good overall yields. Noteworthy is also the fact that the synthetic route is highly flexible, allowing for fine-tuning of the ligand structure. From a preliminary investigation, promising results were obtained when the copper complex derived from the *tert*-butyl derivative *ent*-**19** was employed as catalyst in the enantioselective cyclopropanation of styrene. Further studies toward modification of the ligand structure and investigations of additional catalytic reactions are currently in progress and will be reported in due course.[32]

4. Experimental

4.1. General information

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. THF was distilled from sodium benzophenone ketyl radical, CH_2Cl_2 from CaH_2 under Ar. All other solvents were of reagent grade and used as received. Unless otherwise noted all reactions were carried out under argon using standard Schlenk and vacuum line techniques. For the determination of the enantiomeric ratios of the methyl hemiesters **9** and *ent*-**9**, obtained by asymmetric anhydride opening, see Ref. 11b. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini 300 or Inova 400 spectrometer and were recorded relative to TMS as internal standard. Mass spectra were measured on a Finnigan SSQ 7000 instrument or on a Hewlett Packard GC–MS apparatus-system (column HP-5 MS, 30 m × 0.25 mm × 0.25 μm; mass selective detector 5973). Melting points were measured in open glass capillaries with a Büchi apparatus and are uncorrected. Optical rotations were determined on a Perkin Elmer P241 instrument at room temperature (ca. 20 °C) using solvents of Merck UVASOL-quality. Infrared spectra were recorded on a Perkin Elmer 1760 FT apparatus. All microanalyses were conducted on a Heraeus CHN RAPID instrument at the Institut für Organische Chemie der RWTH Aachen.

4.2. General procedure for the selective ester epimerization GP-1

A freshly prepared LDA solution (3.0 equiv) in absolute THF (0.75 mL/mmol LDA) was added dropwise, over 1.5 h, to a stirred solution of the *cis* monomethylester in absolute THF (1.5 mL/mmol) at −78 °C under argon. After the complete addition, the mixture was stirred at this temperature for 4 h, acidified with 4 N aq HCl and extracted with ethylacetate. The combined organic phases were dried over $MgSO_4$, concentrated, and the residue was purified by column chromatography.

4.2.1. (1*R*,2*R*)-2-Methoxycarbonylcyclopentane-1-carboxylic acid 10. The product was prepared according to GP-1 from the *cis* hemiester **9** (5.165 g, 30.00 mmol). Purification by column chromatography (pentane–Et_2O, 4:1) yielded 4.135 g (24.02 mmol, 80%) of the title compound as a colorless oil: $[\alpha]_D^{rt} = -83.6$ (*c* 3.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72–1.94 (m, 4H), 2.05–2.16 (m, 2H), 3.12–3.22 (m, 2H), 3.72 (s, 3H), 10.70 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 30.3, 30.6, 46.8, 47.0, 52.0, 175.1, 180.6; IR (capillary): 2959, 2878, 1736, 1708, 1439, 1298, 1203 cm^{-1}; EI-MS: m/z = 173 (M^++1, <2), 154 (43), 141 (M^+−31, 40), 126 (70), 112 (45), 95 (50), 67 (100), 55 (15). Anal. Calcd for $C_8H_{12}O_4$ (172.18): C, 55.81; H, 7.02. Found: C, 55.84; H, 6.88.

4.2.2. (1*S*,2*S*)-2-Methoxycarbonylcyclopentane-1-carboxylic acid *ent*-10. The product was prepared according to GP-1 from the *cis* hemiester *ent*-**9**. Purification by column chromatography (pentane–Et_2O, 4:1) yielded 2.035 g (11.82 mmol, 76%) of the title compound as a colorless oil: $[\alpha]_D^{rt} = +81.0$ (*c* 1.07, $CHCl_3$); lit.[28] $[\alpha]_D^{rt} = +84.0$ (*c* 0.60, MeOH).

4.3. General procedure for the synthesis of monoamido esters GP-2

Oxalyl chloride (1.5 equiv) was added dropwise with gas evolution to a cooled solution (0 °C, ice bath) of the *trans* hemiester and dimethylformamide (7 mol %) in CH_2Cl_2 (4.0 mL/mmol) under argon. The reaction mixture was stirred for 1 h at rt, followed by removal of the solvent and excess oxalyl chloride in high vacuum. The residue was taken up in CH_2Cl_2 (3.0 mL/mmol) and added via syringe to a cooled solution (0 °C) of the corresponding amino alcohol (1.1 equiv) and Et_3N (2.5 equiv) in CH_2Cl_2 (4.0 mL/mmol) under argon. After stirring at rt overnight, the reaction mixture was acidified with 2 N HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the crude product, which was purified by column chromatography.

4.3.1. (1*S*,2*S*)-2-[2′-Hydroxy-1′-(*S*)-*tert*-butylethylcarbamoyl]-cyclopentane-1-carboxylic acid methyl ester 20. The product was synthesized from the *trans* hemiester *ent*-**10** (4.821 g, 28.00 mmol) and (*S*)-*tert*-leucinol (3.610 g, 30.80 mmol) according to GP-2. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 6.582 g (24.26 mmol, 87%) of the title compound as a white solid: mp 137–138 °C; $[\alpha]_D^{rt} = +36.1$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (s, 9H), 1.67–1.86 (m, 3H), 1.91–2.01 (m, 2H), 2.07–2.15 (m, 1H), 2.70 (br s, 1H), 2.88 (q, $J = 8.8$ Hz, 1H), 3.10 (q, $J = 8.8$ Hz, 1H), 3.52 (dt, $J = 3.0$, 9.1 Hz, 1H), 3.71 (s, 3H), 3.80–3.85 (m, 2H), 6.16 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.1$, 26.8, 29.8, 30.0, 33.3, 48.3, 48.8, 52.1, 59.8, 63.0, 175.3, 176.1; IR (KBr): 3304, 3248, 3086, 2873, 1734, 1636, 1567, 1432, 1356, 1193, 1174, 1055 cm^{-1}; EI-MS: $m/z = 272$ (M^++H, 7), 240 (100), 214 (22), 196 (13), 182 (7), 155 (29), 127 (7), 95 (21), 86 (70), 67 (19). Anal. Calcd for $C_{14}H_{25}NO_4$ (271.35): C, 61.97; H, 9.29; N, 5.16. Found: C, 62.05; H, 9.05; N, 5.04.

4.3.2. (1*R*,2*R*)-2-[2′-Hydroxy-1′-(*S*)-*tert*-butylethylcarbamoyl]-cyclopentane-1-carboxylic acid methyl ester 30. The product was synthesized from the *trans* hemiester **10** (1.378 g, 8.00 mmol) and (*S*)-*tert*-leucinol (1.031 g, 8.80 mmol) according to GP-2. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 6.582 g (6.53 mmol, 82%) of the title compound as a white solid: mp 101–102 °C; $[\alpha]_D^{rt} = -68.2$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (s, 9H), 1.69–1.97 (m, 4H), 2.00–2.13 (m, 2H), 2.60 (br s, 1H), 2.90–3.02 (m, 2H), 3.54 (dd, $J = 8.0$, 10.7 Hz, 1H), 3.71 (s, 3H), 3.80–3.88 (m, 2H), 6.18 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.3$, 26.8, 29.4, 30.6, 33.4, 48.5, 48.5, 52.0, 59.8, 63.4, 175.3, 175.9; IR (KBr): 3266, 2957, 2873, 1741, 1642, 1568, 1442, 1348, 1267, 1234, 1200, 1143, 1054 cm^{-1}; EI-MS: $m/z = 272$ (M^++H, 24), 240 (M^+−31, 100), 214 (24), 196 (18), 182 (10), 155 (28), 127 (9), 95 (25), 86 (83), 67 (23). Anal. Calcd for $C_{14}H_{25}NO_4$ (271.35): C, 61.97; H, 9.29; N, 5.16. Found: C, 61.80; H, 9.46; N, 4.98.

4.3.3. (1*R*,2*R*)-2-[2′-Hydroxy-1′-(*R*)-phenylethylcarbamoyl]-cyclopentane-1-carboxylic acid methyl ester 26. The product was synthesized from the *trans* hemiester **10** (3.444 g, 20.00 mmol) and (*R*)-phenylglycinol (3.018 g, 22.00 mmol) according to GP-2. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 4.667 g (16.02 mmol, 80%) of the title compound as a white solid: mp 101–102 °C; $[\alpha]_D^{rt} = -84.0$ (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.58$–1.90 (m, 2H), 1.98–2.07 (m, 2H), 2.84 (q, $J = 8.5$ Hz, 1H), 3.01 (t, $J = 5.5$ Hz, 1H), 3.05 (q, $J = 8.5$ Hz, 1H), 3.63 (s, 3H), 3.71–3.77 (m, 2H), 4.98 (dt, $J = 4.4$, 7.2 Hz, 1H), 6.64 (d, $J = 7.2$ Hz, 1H), 7.19–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.4$, 30.2, 30.4, 48.2, 48.7, 52.2, 56.0, 66.6, 126.7, 127.8, 128.8, 139.1, 174.7, 176.1; IR (KBr): 3255, 3081, 3031, 2956, 1731, 1638, 1570, 1453, 1439, 1257, 1199, 1172, 1083, 1047 cm^{-1}; EI-MS: $m/z = 260$ (M^+−31, 74); 200 (3), 155 (8), 127 (4), 120 (6), 106 (100), 95 (17), 67 (17). Anal. Calcd for $C_{16}H_{21}NO_4$ (291.34): C, 65.96; H, 7.27; N, 4.81. Found: C, 65.95; H, 7.04; N, 4.81.

4.4. General procedure for the ester hydrolyses GP-3

A solution of the corresponding methyl ester in MeOH (4.0 mL/mmol) was treated with NaOH (1 N, 3.0 equiv) and stirred at rt for 4 h. The mixture was acidified with 2 N HCl and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to provide the desired product. The product obtained by this way was used in the next step without further purification.

4.4.1. (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylic acid 11. It was synthesized from *trans* hemiester **10** (4.305 g, 25.00 mmol) according to GP-3. The product was obtained as a white solid in 97% yield (3.835 g, 24.25 mmol): mp 184–185 °C; lit.:[29a] mp 160–161 °C; $[\alpha]_D^{rt} = -75.7$ (*c* 0.65, acetone); lit.[29b] $[\alpha]_D^{rt} = -81.0$ (*c* 8.70, H_2O); ^{1}H NMR (400 MHz, acetone-d_6): $\delta = 1.55$–1.62 (m, 2H), 1.65–1.74 (m, 2H), 1.89–1.97 (m, 2H), 2.95–3.01 (m, 2H), 10.20 (br s, 2H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 25.5$, 30.5, 47.0, 175.5; IR (KBr): 2985, 2887, 2663, 1704, 1420, 1287, 1223 cm^{-1}; EI-MS: $m/z = 159$ (M^++1, <2), 140 (41), 112 (100), 99 (29), 95 (29), 86 (11), 67 (99), 55 (16). Anal. Calcd for $C_7H_{10}O_4$ (158.15): C, 53.16; H, 6.37. Found: C, 53.17; H, 6.41.

4.4.2. (1*S*,2*S*)-Cyclopentane-1,2-dicarboxylic acid *ent*-11. It was synthesized from *trans* hemiester *ent*-**10** (1.722 g, 10.00 mmol) according to GP-3. The product was obtained as a white solid in 95% yield (1.498 g,

9.47 mmol): lit.:[28] mp 183–185 °C; lit.:[29c] mp 180–181 °C; $[\alpha]_D^{rt} = +73.5$ (*c* 1.00, acetone); lit.[28] $[\alpha]_D^{rt} = +81.0$ (*c* 1.40, MeOH); lit.[29c] $[\alpha]_D^{rt} = +87.6$ (MeOH).

4.4.3. (1*S*,2*S*)-2-[2′-Hydroxy-1′-(*S*)-*tert*-butylethylcarbamoyl]-cyclopentane-1-carboxylic acid 22. The title compound was synthesized from **20** (3.528 g, 13.00 mmol) according to GP-3. The product was obtained as a white solid in 95% yield (3.177 g, 12.34 mmol): mp 147 °C; $[\alpha]_D^{rt} = +46.5$ (*c* 1.03, acetone); ^{1}H NMR (400 MHz, acetone-d_6): $\delta = 0.92$ (s, 9H), 1.60–1.75 (m, 2H), 1.77–1.89 (m, 2H), 1.94–2.06 (m, 2H), 2.98 (q, $J = 8.5$ Hz, 1H), 3.10 (q, $J = 8.5$ Hz, 1H), 3.51 (dd, $J = 8.0$, 11.3 Hz, 1H), 3.70 (dd, $J = 3.8$, 11.3 Hz, 1H), (3.51/3.70 AB part of an ABX-system), 3.81 (ddd, $J = 3.8$, 8.0, 9.6 Hz, 1H), 6.90 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 25.1$, 26.5, 29.6, 31.0, 33.7, 47.1, 48.6, 59.4, 61.6, 174.9, 175.6; IR (KBr): 3244, 3088, 2961, 2872, 1701, 1637, 1569, 1369, 1295, 1250, 1054 cm^{-1}; EI-MS: $m/z = 226$ (M^+-31, 86), 200 (34), 182 (16), 141 (13), 95 (21), 86 (100), 67 (22), 60 (58). Anal. Calcd for $C_{13}H_{23}NO_4$ (257.33): C, 60.68; H, 9.01; N, 5.44. Found: C, 60.32; H, 8.77; N, 5.45.

4.4.4. (1*R*,2*R*)-2-[2′-Hydroxy-1′-(*S*)-*tert*-butylethylcarbamoyl]-cyclopentane-1-carboxylic acid 31. The title compound was synthesized from **30** (1.357 g, 5.00 mmol) according to GP-3. The product was obtained as a white solid in 98% yield (1.265 g, 4.92 mmol): mp 134–135 °C; $[\alpha]_D^{rt} = -55.9$ (*c* 0.56, acetone); ^{1}H NMR (400 MHz, acetone-d_6): $\delta = 0.94$ (s, 9H), 1.63–2.10 (m, 6H), 3.00 (q, $J = 8.2$ Hz, 1H), 3.06 (q, $J = 8.2$ Hz, 1H), 3.55 (dd, $J = 7.7$, 11.3 Hz, 1H), 3.74 (dd, $J = 3.8$, 11.3 Hz, 1H), (3.55/3.74 AB part of an ABX-system), 3.82 (dd, $J = 3.8$, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 26.0$, 27.3, 30.9, 31.2, 34.5, 48.3, 49.3, 59.8, 62.2, 175.4, 176.3; IR (KBr): 3462, 3287, 2960, 2876, 1710, 1619, 1585, 1473, 1424, 1395, 1246, 1222, 1057 cm^{-1}; EI-MS: $m/z = 258$ (M^++1, 19), 226 (M^+-31, 91), 208 (11), 200 (30), 182 (17), 141 (10), 95 (18), 86 (100), 67 (22), 60 (57). Anal. Calcd for $C_{13}H_{23}NO_4$ (257.33): C, 60.68; H, 9.01; N, 5.44. Found: C: 60.42; H, 9.24; N, 5.25.

4.4.5. (1*R*,2*R*)-2-[2′-Hydroxy-1′-(*R*)-phenylethylcarbamoyl]-cyclopentane-1-carboxylic acid 27. The title compound was synthesized from **26** (4.224 g, 14.50 mmol) according to GP-3. The product was obtained as a white solid in 97% yield (3.893 g, 14.04 mmol): mp 133–134 °C; $[\alpha]_D^{rt} = -96.9$ (*c* 1.00, acetone); ^{1}H NMR (400 MHz, acetone-d_6): $\delta = 1.58$–1.79 (m, 3H), 1.82–1.90 (m, 1H), 1.96–2.09 (m, 2H), 3.07 (q, $J = 8.0$ Hz, 1H), 3.14 (q, $J = 8.0$ Hz, 1H), 3.74–3.78 (m, 2H), 5.02–5.07 (m, 1H), 7.21–7.40 (m, 5H), 7.58 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 26.0$, 30.6, 31.6, 47.6, 49.1, 56.5, 66.2, 127.6, 127.6, 128.8, 141.7, 174.8, 176.2; IR (KBr): 3302, 2956, 2870, 1701, 1652, 1548, 1452, 1387, 1301, 1270, 1051 cm^{-1}; EI-MS: $m/z = 246$ (M^+-31, 61); 201 (5), 141 (4), 120 (7), 106 (100), 95 (11), 67 (12). Anal. Calcd for $C_{15}H_{19}NO_4$ (277.32): C, 64.95; H, 6.91; N, 5.05. Found: C, 64.57; H, 6.89; N, 4.94.

4.5. General procedure for the synthesis of various C_2-symmetric bis(hydroxyamides) GP-4

Oxalyl chloride (3.0 equiv) was added dropwise to a cooled suspension (0 °C) of the *trans* diacid (1.0 equiv) and dimethylformamide (15 mol %) in CH_2Cl_2 (5.0 mL/mmol) under argon. Gas evolution was accompanied by the formation of a clear, pale yellow solution, which was stirred at rt for 1 h. The solvent and excess oxalyl chloride were removed in high vacuum, the solid residue was taken up in CH_2Cl_2 (4.0 mL/mmol) and added slowly, via syringe, to a cooled solution (0 °C) of the corresponding amino alcohol (2.2 equiv) and Et_3N (5.0 equiv) in CH_2Cl_2 (2.0 mL/mmol) under argon. Stirring was continued for 16 h at rt, and it was accompanied by the formation of a white solid. The solid was filtered, washed with CH_2Cl_2, and dried in high vacuum to provide the corresponding bis(hydroxyamide).

4.5.1. (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylic acid bis-[(2′-hydroxy-1′-(*R*)-phenylethyl)-amide] 12. It was synthesized according to GP-4 from (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid **11** (1.58 g, 10.00 mmol) and (*R*)-phenylglycinol (3.018 g, 22.00 mmol). The product was obtained in 62% yield (2.466 g, 6.22 mmol) as a white solid: mp (dec) 240–243 °C; $[\alpha]_D^{rt} = -162.5$ (*c* 1.00, DMSO); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 1.68$–1.75 (m, 4H), 1.96–2.01 (m, 2H), 3.00–3.04 (m, 2H), 3.68 (dd, $J = 7.7$, 11.3 Hz, 2H), 3.73 (dd, $J = 5.2$, 11.3 Hz, 2H), 4.98 (dd, $J = 5.2$, 7.7 Hz, 2H), 3.68/3.73/4.98 (ABX-system), 7.20–7.25 (m, 2H), 7.30 (d, $J = 4.4$ Hz, 8H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 25.5$, 31.0, 49.2, 56.0, 65.1, 126.7, 127.1, 128.3, 140.0, 176.0; IR (KBr): 3310, 2957, 1647, 1547, 1039 cm^{-1}; EI-MS: $m/z = 365$ (M^+-31, 100), 260 (56), 233 (12), 167 (12), 140 (49), 121 (43), 106 (84), 95 (14). Anal. Calcd for $C_{23}H_{28}N_2O_4$ (396.48): C, 69.67; H, 7.12; N, 7.07. Found: C, 69.43; H, 7.13; N, 7.03.

4.5.2. (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylic acid bis-[(2′-hydroxy-1′-(*S*)-phenylethyl)-amide] 13. It was synthesized according to GP-4 from (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid **11** (1.58 g, 10.00 mmol) and (*S*)-phenylglycinol (3.018 g, 22.00 mmol). The product was isolated in 70% yield (2.780 g, 7.01 mmol) as a white solid: mp (dec) 235–237 °C; $[\alpha]_D^{rt} = +31.5$ (*c* 1.10, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.58$–1.71 (m, 4H), 1.91–1.97 (m, 2H), 2.92–2.98 (m, 2H), 3.47 (dd, $J = 6.9$, 11.0 Hz, 2H), 3.53 (dd, $J = 5.8$, 11.0 Hz, 2H), (3.47/3.53 AB part of an ABX-system), 4.79 (t, $J = 5.8$ Hz, 2H), 4.81 (q, $J = 8.0$ Hz, 2H), 7.16–7.23 (m, 10H), 8.02 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 25.3$, 31.2, 47.5, 58.8, 64.5, 126.2, 126.5, 127.6, 140.9, 173.6; IR (KBr): 3296, 3066, 2951, 2871, 1645, 1618, 1547, 1251, 1051 cm^{-1}; EI-MS: $m/z = 365$ (M^+-31, 100), 260 (53), 233 (8), 167 (12), 140 (68), 121 (40), 106 (73), 95 (15). Anal. Calcd for $C_{23}H_{28}N_2O_4$ (396.48): C, 69.67; H, 7.12; N, 7.07. Found: C, 69.71; H, 7.40; N, 6.95.

4.5.3. (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylic acid bis-[(2′-hydroxy-1′-(*S*)-*tert*-butylethyl)-amide] 14. It was synthesized according to GP-4 from (1*R*,2*R*)-cyclopen-

tane-1,2-dicarboxylic acid **11** (1.58 g, 10.00 mmol) and (*S*)-*tert*-leucinol (2.578 g, 22.00 mmol). The product was isolated in 70% yield (2.511 g, 7.04 mmol) as a white solid: mp 210–213 °C; $[\alpha]_D^{rt} = -42.7$ (*c* 1.10, MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.90$ (s, 18H), 1.71–1.85 (m, 4H), 2.06–2.12 (m, 2H), 3.00–3.07 (m, 2H), 3.44 (dd, $J = 9.6$, 12.1 Hz, 2H), 3.74–3.80 (m, 4H), 7.52 (d, $J = 9.4$ Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 25.5$, 26.2, 31.6, 33.5, 49.1, 59.6, 61.2, 176.6; IR (KBr): 3319, 2959, 2875, 1649, 1547, 1475, 1369, 1245, 1054 cm^{-1}; EI-MS: $m/z = 357$ (M^++H, 3), 325 (M^+−31, 56), 299 (17), 281 (14), 263 (12), 240 (100), 222 (7), 212 (6), 194 (3), 140 (6), 100 (9), 86 (16). Anal. Calcd for $C_{19}H_{36}N_2O_4$ (356.50): C, 64.01; H, 10.18; N, 7.86. Found: C, 63.92; H, 10.13; N, 7.80.

4.5.4. (1*S*,2*S*)-Cyclopentane-1,2-dicarboxylic acid bis-[(2′-hydroxy-1′-(*S*)-*tert*-butylethyl)-amide] *ent*-15. It was synthesized according to GP-4 from (1*S*,2*S*)-cyclopentane-1,2-dicarboxylic acid *ent*-**11** (0.79 g, 5.00 mmol) and (*S*)-*tert*-leucinol (1.289 g, 11.00 mmol). The product was isolated in 65% yield (1.163 g, 3.26 mmol) as a white solid: mp (dec) >250 °C; $[\alpha]_D^{rt} = +76.6$ (*c* 0.50, MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 0.95$ (s, 9H), 1.77–2.08 (m, 6H), 2.95–3.04 (m, 2H), 3.40–3.48 (m, 2H), 3.78–3.86 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 25.6$, 25.8, 30.6, 33.2, 49.4, 59.6, 60.7, 176.8; IR (KBr): 3291, 2957, 2871, 1640, 1555, 1461, 1397, 1368, 1249, 1050, 1023 cm^{-1}; EI-MS: $m/z = 357$ (M^++H, 7), 325 (M^+−31, 53), 299 (15), 281 (14), 263 (21), 240 (100), 222 (11), 212 (7), 194 (6), 140 (8), 100 (8), 86 (15). Anal. Calcd for $C_{19}H_{36}N_2O_4$ (356.50): C, 64.01; H, 10.18; N, 7.86. Found: C, 63.70; H, 10.41; N, 7.60.

4.6. GP-5

Solid EEDQ (1.2 equiv) was added at 0 °C to a solution of the monoamido acid (1.0 equiv) and the corresponding amino alcohol (1.0 equiv) in dry THF (10.0 mL/mmol) and the mixture were stirred at rt for 5 days. The solvent was removed in vacuum and the crude reaction product was purified by column chromatography.

4.6.1. (1*S*,2*S*)-Cyclopentane-1,2-dicarboxylic acid 1-[(2′-hydroxy-1′-(*S*)-*tert*-butylethyl)-amide]-2-[(2″-hydroxy-1″-(*S*)-phenylethyl)-amide] 21. The product was synthesized from **22** (1.80 g, 7.00 mmol) and (*S*)-phenylglycinol (0.960 g, 7.00 mmol) according to GP-5. Purification by column chromatography (pentane–EtOAc, 1:1 + 5% MeOH) delivered the title compound as a white solid in 83% yield (2.190 g, 5.82 mmol): mp 185–188 °C; $[\alpha]_D^{rt} = +117.2$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.92$ (s, 9H), 1.71–1.86 (m, 4H), 1.96–2.05 (m, 2H), 2.99 (q, $J = 8.0$ Hz, 1H), 3.05 (q, $J = 8.0$ Hz, 1H), 3.46 (dd, $J = 8.8$, 11.0 Hz, 1H), 3.66 (dd, $J = 8.2$, 11.5 Hz, 1H), 3.73 (dd, $J = 5.0$, 11.5 Hz, 1H), (3.66/3.73 AB part of an ABX-system), 3.77–3.84 (m, 2H), 5.01 (dd, $J = 5.0$, 8.2 Hz, 1H), 7.22–7.26 (m, 1H), 7.31 (d, $J = 4.4$ Hz, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 25.6$, 26.0, 30.5, 31.2, 33.4, 49.0, 49.5, 55.8, 59.6, 61.0, 64.9, 126.5, 127.0, 128.1, 139.8, 175.9, 176.5; IR (KBr): 3291, 2959, 1640, 1553, 1249, 1050 cm^{-1}; EI-MS: $m/z = 345$ (M^+−31, 100), 327 (7), 319 (13), 260 (40), 240 (76), 213 (14), 194 (8), 157 (8), 140 (41), 121 (23), 106 (52), 95 (18), 86 (23). Anal. Calcd for $C_{21}H_{32}N_2O_4$ (376.49): C, 66.99; H, 8.57; N, 7.44. Found: C, 66.96; H, 8.58; N, 7.26.

4.6.2. (1*S*,2*S*)-Cyclopentane-1,2-dicarboxylic acid 1-[(2′-hydroxy-1′-(*S*)-*tert*-butylethyl)-amide]-2-[(2″-hydroxy-1″-(*R*)-phenylethyl)-amide] 23. The product was synthesized from **22** (1.80 g, 7.00 mmol) and (*R*)-phenylglycinol (0.960 g, 7.00 mmol) according to GP-5. Purification by column chromatography (pentane–EtOAc, 1:1 + 5% MeOH) delivered the title compound as a white solid in 86% yield (2.281 g, 6.06 mmol): mp 143.5–145 °C; $[\alpha]_D^{rt} = +4.2$ (*c* 1.15, MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 0.90$ (s, 9H), 1.71–1.91 (m, 4H), 1.99–2.13 (m, 2H), 2.97 (q, $J = 8.2$ Hz, 1H), 3.12 (q, $J = 8.2$ Hz, 1H), 3.38 (dd, $J = 8.4$, 11.4 Hz, 1H), 3.64–3.78 (m, 4H), 4.94 (dd, $J = 5.4$, 7.4 Hz, 1H), 7.20–7.27 (m, 1H), 7.31 (d, $J = 4.4$ Hz, 4H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 25.1$, 25.9, 30.6, 31.5, 33.4, 48.2, 48.9, 55.8, 59.3, 61.2, 64.8, 126.6, 126.8, 128.1, 139.8, 176.1, 176.2; IR (KBr): 3308, 2960, 2873, 1646, 1544, 1457, 1368, 1244, 1049 cm^{-1}; EI-MS: $m/z = 345$ (M^+−31, 100), 327 (8), 319 (13), 260 (36), 240 (69), 213 (8), 194 (6), 157 (8), 140 (50), 121 (26), 106 (42), 95 (18), 86 (22). HRMS for $C_{21}H_{32}N_2O_4$–CH_2OH^+: calcd 345.2178; found: 345.2178.

4.6.3. (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylic acid 1-[(2′-hydroxy-1′-(*S*)-*tert*-butylethyl)-amide]-2-[(2″-hydroxy-1″-(*R*)-phenylethyl)-amide] 28. The product was synthesized from **27** (1.941 g, 7.00 mmol) and (*S*)-*tert*-leucinol (0.820 g, 7.00 mmol) according to GP-5. Purification by column chromatography (pentane–EtOAc, 1:1 + 5% MeOH) delivered the title compound as a white solid in 81% yield (2.131 g, 5.66 mmol): mp 158–160 °C; $[\alpha]_D^{rt} = -135.5$ (*c* 0.40, MeOH); ^{1}H NMR (400 MHz, CD_3OD): $\delta = 0.94$ (s, 9H), 1.62–1.92 (m, 4H), 1.99–2.12 (m, 2H), 2.97–3.09 (m, 2H), 3.48 (dd, $J = 9.3$, 12.1 Hz, 1H), 3.70 (dd, $J = 6.3$, 11.3 Hz, 1H), 3.73 (dd, $J = 6.9$, 11.3 Hz, 1H), (3.70/3.73 AB part of an ABX-system), 3.77–3.81 (m, 2H), 4.95 (t, $J = 6.3$ Hz, 1H), 7.24–7.32 (m, 1H), 7.33 (d, $J = 4.4$ Hz, 4H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 24.9$, 26.1, 30.3, 31.4, 33.5, 48.8, 49.6, 55.7, 59.4, 61.1, 64.8, 126.6, 126.9, 128.0, 140.0, 175.3, 176.2; IR (KBr): 3275, 3083, 2960, 2872, 1635, 1554, 1455, 1368, 1351, 1243, 1051 cm^{-1}; EI-MS: $m/z = 345$ (M^+−31, 100), 327 (8), 319 (14), 260 (39), 240 (74), 213 (12), 194 (9), 157 (8), 140 (42), 121 (29), 106 (53), 95 (19), 86 (20). Anal. Calcd for $C_{21}H_{32}N_2O_4$ (376.49): C, 66.99; H, 8.57; N, 7.44. Found: C, 66.88; H, 8.42; N, 7.34.

4.6.4. (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylic acid 1-[(2′-hydroxy-1′-(*S*)-*tert*-butylethyl)-amide]-2-[(2″-hydroxy-1″-(*S*)-phenylethyl)-amide] 32. The product was synthesized from **31** (1.029 g, 4.00 mmol) and (*S*)-phenylglycinol (0.549 g, 4.00 mmol) according to GP-5. Purification by column chromatography (pentane–EtOAc, 1:1 + 5% MeOH) delivered the title compound as a white solid in 83% yield (1.250 g, 3.32 mmol): mp 207 °C; $[\alpha]_D^{rt} = +6.0$ (*c* 1.00, MeOH); ^{1}H NMR

(400 MHz, CD_3OD): $\delta = 0.74$ (s, 9H), 1.75–1.92 (m, 4H), 1.99–2.07 (m, 1H), 2.11–2.18 (m, 1H), 2.96–3.05 (m, 2H), 3.36–3.43 (m, 1H), 3.69 (dd, $J = 7.4$, 11.3 Hz, 1H), 3.74 (dd, $J = 5.5$, 11.3 Hz, 1H), 3.69/3.74 (AB part of an ABX-system), 3.68–3.74 (m, 2H), 4.99 (dd, $J = 5.5$, 7.4 Hz, 1H), 7.22–7.32 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 25.2$, 26.0, 30.6, 31.8, 33.3, 48.7, 49.6, 55.8, 59.4, 61.0, 64.9, 126.8, 126.9, 128.0, 139.8, 175.6, 176.1; IR (KBr): 3317, 2961, 2872, 1623, 1540, 1368, 1253, 1086, 1049 cm^{-1}; EI-MS: $m/z = 377$ (M^++1, 4), 345 (M^+−31, 100), 327 (9), 319 (14), 260 (29), 240 (54), 194 (4), 157 (6), 140 (35), 121 (16), 106 (25), 95 (10), 86 (12). Anal. Calcd for $C_{21}H_{32}N_2O_4$ (376.49): C, 66.99; H, 8.57; N, 7.44. Found: C, 66.79; H, 8.83; N, 7.48.

4.7. General procedure for the preparation of various C_2- and C_1-symmetric bisoxazolines with cyclopentane as backbone GP-7

Diethylaminosulfur trifluoride (0.67 mL, 5.50 mmol, 2.2 equiv) was added dropwise to a cooled (−78 °C) suspension of the corresponding bis-hydroxyamide (2.50 mmol) in dry CH_2Cl_2 (25.0 mL). After stirring for 3–5 h at the indicated temperature, anhydrous K_2CO_3 (1.04 g, 7.50 mmol, 3.0 equiv) was added and the reaction mixture was allowed to warm to rt. A saturated aq $NaHCO_3$ solution was added and after phase separation the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuum to yield the crude product, which was purified by column chromatography.

4.7.1. (1*R*,2*R*)-Bis-[4′-(*R*)-phenyloxazolin-2′-′yl]-cyclopentane 16.

The product was synthesized from **12** (0.991 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 0.818 g (2.27 mmol, 90%) of the title compound as a colorless oil: $[\alpha]_D^{rt} = -20.8$ (c 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.72$–1.82 (m, 2H), 1.86–1.98 (m, 2H), 2.06–2.17 (m, 2H), 3.20–3.30 (m, 2H), 4.02 (t, $J = 8.2$ Hz, 2H), 4.54 (dd, $J = 8.2$, 10.1 Hz, 2H), 5.10 (dd, $J = 7.9$, 10.1 Hz, 2H), 7.13–7.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.5$, 31.3, 42.6, 69.6, 75.0, 126.7, 127.5, 128.7, 142.7, 170.3; IR (capillary): 3061, 3029, 2962, 2899, 1660, 1493, 1453, 1360, 1177, 1079 cm^{-1}; EI-MS: $m/z = 360$ (M^+, 96), 242 (59), 214 (100), 199 (15), 187 (20), 174 (45), 120 (12), 104 (48), 95 (21), 91 (27), 67 (17). HRMS for $C_{23}H_{24}N_2O_2$: calcd 360.1838; found: 360.1838.

4.7.2. (1*R*,2*R*)-Bis-[4′-(*R*)-phenyloxazolin-2′-yl]-cyclopentane 17.

The product was synthesized from **13** (0.991 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 0.721 g (2.00 mmol, 80%) of the title compound as a colorless oil: $[\alpha]_D^{rt} = -189.6$ (c 3.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.80$–1.89 (m, 2H), 1.95–2.04 (m, 2H), 2.15–2.23 (m, 2H), 3.28–3.35 (m, 2H), 4.09 (t, $J = 8.2$ Hz, 2H), 4.63 (dd, $J = 8.5$, 10.2 Hz, 2H), 5.18 (dd, $J = 8.0$, 10.2 Hz, 2H), 7.22–7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.5$, 31.2, 42.6, 69.6, 75.1, 126.6, 127.5, 128.7, 142.5, 170.5; IR (in $CHCl_3$): 2964, 2900, 1660, 1494, 1453, 1359, 1176, 1026 cm^{-1}; EI-MS: $m/z = 360$ (M^+, 96), 242 (48), 214 (100), 199 (16), 187 (24), 174 (55), 120 (54), 104 (51), 95 (21), 91 (26), 67 (17). HRMS for $C_{23}H_{24}N_2O_2$: calcd 360.1838; found: 360.1838.

4.7.3. (1*R*,2*R*)-Bis-[4′-(*S*)-*tert*-butyloxazolin-2′-yl]-cyclopentane 18.

The product was synthesized from **14** (0.891 g, 2.5 mmol) according to GP-7. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 0.742 g (2.31 mmol, 92% yield) of the title compound as a white solid: mp 53.5–54.5 °C; $[\alpha]_D^{rt} = -186.9$ (c 1.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (s, 18H), 1.72–1.89 (m, 4H), 2.02–2.10 (m, 2H), 3.13 (t, $J = 5.8$ Hz, 2H), 3.79 (dd, $J = 7.4$, 9.9 Hz, 2H), 4.04 (dd, $J = 7.4$, 8.5 Hz, 2H), 4.12 (dd, $J = 8.5$, 9.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.4$, 25.7, 31.3, 33.7, 42.0, 68.5, 75.3, 168.7; IR (KBr): 2959, 2905, 2869, 1670, 1480, 1359, 1258, 1229, 1019 cm^{-1}; EI-MS: $m/z = 320$ (M^+, 14), 305 (6), 263 (100), 205 (6), 194 (15), 163 (24), 136 (21), 95 (2), 67 (3). Anal. Calcd for $C_{19}H_{32}N_2O_2$ (320.47): C, 71.21; H, 10.06; N, 8.74. Found: C, 70.81; H, 9.74; N, 8.68.

4.7.4. (1*S*,2*S*)-Bis-[4′-(*S*)-*tert*-butyloxazolin-2′-yl]-cyclopentane *ent*-19.

The product was synthesized from *ent*-**15** (0.891 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 0.663 g (2.07 mmol, 83%) of the title compound as a white solid: mp 51 °C; $[\alpha]_D^{rt} = +2.5$ (c 0.69, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (s, 18H), 1.70–1.77 (m, 2H), 1.81–1.89 (m, 2H), 2.00–2.08 (m, 2H), 3.09–3.16 (m, 2H), 3.80 (dd, $J = 7.4$, 10.2 Hz, 2H), 4.03 (dd, $J = 7.4$, 8.5 Hz, 2H), 4.12 (dd, $J = 8.5$, 10.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.4$, 25.7, 31.2, 33.6, 42.1, 68.5, 75.3, 168.5; IR (KBr): 2956, 2902, 2873, 1670, 1476, 1360, 1249, 1188 cm^{-1}; EI-MS: $m/z = 320$ (M^+, 15), 305 (5), 263 (100), 205 (4), 194 (9), 163 (15), 136 (18). HRMS for $C_{19}H_{32}N_2O_2$: calcd 320.2464; found: 320.2464.

4.7.5. (1*S*,2*S*)-[4′-(*S*)-*tert*-Butyloxazolin-2′-yl]-[4″-(*S*)-phenyloxazolin-2″-yl]-cyclopentane 24.

The product was synthesized from **21** (0.941 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 0.705 g (2.07 mmol, 83% yield) of the title compound as a colorless oil: $[\alpha]_D^{rt} = +9.6$ (c 1.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (s, 9H), 1.77–1.98 (m, 4H), 2.04–2.15 (m, 2H), 3.17–3.28 (m, 2H), 3.83 (ddd, $J = 0.8$, 7.7, 10.2 Hz, 1H), 4.06 (dd, $J = 7.7$, 8.8 Hz, 1H), 4.07 (dd, $J = 8.0$, 8.2 Hz, 1H), 4.16 (dd, $J = 8.8$, 10.2 Hz, 1H), 4.59 (dd, $J = 8.2$, 9.9 Hz, 1H), 5.14 (dd, $J = 8.0$, 9.9 Hz, 1H), 7.21–7.28 (m, 3H), 7.30–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.4$, 25.7, 31.1, 31.2, 33.6, 42.1, 42.2, 68.5, 69.4, 74.8, 75.3, 126.4, 127.2, 128.4, 142.4, 168.4, 170.3; IR (capillary): 2957, 2902, 2872, 1664, 1477, 1454, 1361, 1180, 1025 cm^{-1}; EI-MS: $m/z = 340$ (M^+, 39), 325 (4), 283 (100), 242 (11), 214 (29), 163 (55), 136 (34), 120 (13), 103 (7), 95 (8), 67 (8). HRMS for $C_{21}H_{28}N_2O_2$: calcd 340.2151; found: 340.2151.

4.7.6. (1*S*,2*S*)-[4′-(*S*)-*tert*-Butyloxazolin-2′-yl]-[4″-(*R*)-phenyloxazolin-2″-yl]-cyclopentane 25. The product was synthesized from **23** (0.941 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 0.692 g (2.03 mmol, 81%) of the title compound as a white solid: mp 61 °C; $[\alpha]_D^{rt} = +110.2$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (s, 9H), 1.76–2.04 (m, 4H), 2.05–2.18 (m, 2H), 3.15–3.26 (m, 2H), 3.84 (ddd, $J = 0.8$, 7.4, 10.2 Hz, 1H), 4.05 (dd, $J = 8.0$, 8.5 Hz, 1H), 4.06 (dd, $J = 7.4$, 8.5 Hz, 1H), 4.16 (dd, $J = 8.5$, 10.2 Hz, 1H), 4.59 (dd, $J = 8.5$, 10.2 Hz, 1H), 5.14 (dd, $J = 8.0$, 10.2 Hz, 1H), 7.21–7.27 (m, 3H), 7.30–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.3$, 25.9, 31.0, 31.2, 33.8, 42.4, 43.1, 68.8, 69.5, 74.9, 75.6, 126.6, 127.4, 128.6, 142.6, 168.4, 170.5; IR (KBr): 2952, 2874, 1668, 1476, 1451, 1398, 1352, 1245, 1180, 1026, 1004 cm^{-1}; EI-MS: $m/z = 340$ (M^+, 25), 283 (100), 242 (8), 214 (28), 163 (76), 136 (62), 120 (19), 103 (11), 95 (11), 67 (13). Anal. Calcd for $C_{21}H_{28}N_2O_2$ (340.46): C, 74.08; H, 8.29; N, 8.23. Found: C, 73.94; H, 7.95; N, 8.23.

4.7.7. (1*R*,2*R*)-[4′-(*S*)-*tert*-Butyloxazolin-2′-yl]-[4″-(*R*)-phenyloxazolin-2″-yl]-cyclopentane 29. The product was synthesized from **28** (0.941 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 0.712 g (2.09 mmol, 83%) of the title compound as a colorless oil: $[\alpha]_D^{rt} = -96.9$ (*c* 2.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (s, 9H), 1.77–2.00 (m, 4H), 2.07–2.18 (m, 2H), 3.16–3.23 (m, 2H), 3.83 (dd, $J = 7.4$, 10.2 Hz, 1H), 4.06 (dd, $J = 7.4$, 8.5 Hz, 1H), 4.07 (dd, $J = 8.0$, 8.2 Hz, 1H), 4.16 (dd, $J = 8.5$, 10.2 Hz, 1H), 4.59 (dd, $J = 8.2$, 10.2 Hz, 1H), 5.14 (dd, $J = 8.0$, 10.2 Hz, 1H), 7.21–7.28 (m, 3H), 7.30–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.4$, 25.9, 31.1, 31.2, 33.9, 42.6, 42.6, 68.7, 69.6, 75.0, 75.5, 126.6, 127.4, 128.6, 142.6, 168.6, 170.4; IR (capillary): 2957, 2902, 2872, 1665, 1477, 1361, 1180, 1025 cm^{-1}; EI-MS: $m/z = 340$ (M^+, 36), 283 (100), 242 (7), 214 (30), 163 (72), 136 (51), 120 (20), 103 (10), 95 (9), 67 (10). HRMS for $C_{21}H_{28}N_2O_2$: calcd 340.2151; found: 340.2150.

4.7.8. (1*S*,2*S*)-[4′-(*S*)-*tert*-Butyloxazolin-2′-yl]-[4″-(*S*)-phenyloxazolin-2″-yl]-cyclopentane 33. The product was synthesized from **32** (0.941 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane–EtOAc, 1:2) yielded 0.719 g (2.11 mmol, 84% yield) of the title compound as a white solid: mp 36 °C; $[\alpha]_D^{rt} = -197.3$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (s, 9H), 1.77–1.99 (m, 4H), 2.08–2.18 (m, 2H), 3.16–3.26 (m, 2H), 3.82 (dd, $J = 7.1$, 9.9 Hz, 1H), 4.05–4.09 (m, 1H), 4.07 (dd, $J = 7.1$, 8.5 Hz, 1H), 4.16 (dd, $J = 8.5$, 9.9 Hz, 1H), 4.59 (dd, $J = 8.2$, 10.2 Hz, 1H), 5.15 (dd, $J = 8.0$, 10.2 Hz, 1H), 7.21–7.28 (m, 3H), 7.30–7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.5$, 25.9, 31.3, 31.4, 33.9, 42.3, 42.6, 68.7, 69.5, 75.0, 75.5, 126.6, 127.4, 128.6, 142.6, 168.7, 170.6; IR (KBr): 2956, 2904, 2875, 1667, 1360, 1189 cm^{-1}; EI-MS: $m/z = 340$ (M^+, 51), 283 (100), 242 (6), 214 (21), 163 (46), 136 (31), 120 (10), 103 (6), 95 (6), 67 (6). Anal. Calcd for $C_{21}H_{28}N_2O_2$ (340.46): C, 74.08; H, 8.29; N, 8.23. Found: C, 74.14; H, 8.64; N, 8.08.

4.8. Applications in the catalysis

The enantioselective hetero-Diels–Alder and asymmetric transfer hydrogenation reactions were performed according to known literature procedures.[30]

4.8.1. General procedure for the asymmetric cyclopropanation reaction GP-7. A solution of the corresponding ligand *ent*-**19** (4.8 mg, 0.015 mmol, 1.05 mol %) in dry CH_2Cl_2 was added via syringe to a flask containing $CuOTf{\cdot}0.5C_6H_6$ (3.5 mg, 0.014 mmol, 1 mol %) under argon. After stirring at rt for 1 h, the mixture was cooled to 0 °C. Styrene (1.7 mL, 14.00 mmol, 10.0 equiv) was added followed by slow addition of a solution of ethyl diazoacetate (0.16 g, 1.40 mmol in 2.5 mL CH_2Cl_2) over 5 h via syringe pump. The mixture was allowed to warm to rt and it was stirred for an additional 16 h before quenching with a 10% aq solution of NH_4Cl (5.0 mL). The solution was diluted with Et_2O (25.0 mL) and washed with water (5.0 mL) and brine (5.0 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuum to yield the cyclopropanated products as a mixture of cis and trans isomers. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. In order to determine the enantiomer ratios, the cis and trans isomers have been separated by column chromatography (2% ethylacetate in pentane). The enantiomer ratio of the trans isomer was determined by HPLC analysis, while comparison of specific rotation was used for the cis isomer. The absolute configurations of the products were confirmed by the signs of the specific rotations.

Ee = 83% [HPLC analysis: Chiralcel OD-H at rt, *n*-heptane–2-propanol = 95:5, 0.5 mL/min, 254 nm, $t_1 = 9.6$ min (major, (1*R*,2*R*)), $t_2 = 12.0$ min]. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (t, $J = 7.1$ Hz, 3H), 1.29–1.33 (m, 1H), 1.60 (ddd, $J = 4.1$, 5.2, 9.1 Hz, 1H), 1.90 (ddd, $J = 4.1$, 5.2, 8.2 Hz, 1H), 2.51 (ddd, $J = 4.1$, 6.6, 9.3 Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 7.08–7.11 (m, 2H), 7.17–7.22 (m, 1H), 7.25–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 17.0, 24.1, 26.1, 60.6, 126.0, 126.3, 128.3, 139.9, 173.1.

4.8.2. General procedure for the asymmetric Diels–Alder reaction GP-8. A mixture of $Cu(OTf)_2$ or $CuCl_2$ (0.025 mmol, 10 mol %) and the ligand **17** (9.9 mg, 0.0275 mmol, 11 mol %) in dry CH_2Cl_2 was stirred for 2 h at rt under argon. In the case of the counterion screening, silver salts (0.05 mmol) were added to the precursor complex synthesized from $CuCl_2$. Stirring was continued for 30 min and the catalysis was started by adding the dienophile (0.25 mmol), followed by freshly distilled cyclopentadiene. The reaction was monitored by TLC and stopped by filtration through a plug of silica gel using CH_2Cl_2 as solvent. Evaporation of the solvent and purification by column chromatography afforded the product as a white solid. The *endo*/*exo* ratio was determined by ^{1}H NMR analysis of the reaction mixture and confirmed by HPLC analysis. The two

diastereomers were separated by chromatography and the absolute configuration of the *endo* product was assigned by comparison of the sign of the specific rotation with the one reported in the literature.[31]

endo/*exo* = 77:23; ee_{endo} = 71% [HPLC analysis: Chiralcel OD-H at rt, *n*-heptane–2-propanol = 98:2, 1.0 mL/min, 210 nm, t_1 (*exo*) = 27.7 min, t_2 (*endo*, major, (1*S*,2*S*,3*R*,4*R*)) = 32.0 min, t_2 (*endo*, minor) = 34.9 min].

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