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Novel chiral bis(oxazolines): synthesis and application as ligands in the copper-catalyzed enantioselective conjugate addition of diethylzinc to enones

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Abstract—Novel chiral C_2-symmetric bis(oxazolines) were prepared from tartaric acid. They were applied as ligands in the copper-catalyzed conjugate addition of diethylzinc to chalcone and 2-cyclohexenone. Maximum enantiomeric excesses of 50% and 53% were obtained, respectively. The sense of induction was found to depend on the configuration of the stereogenic centre in the oxazoline ring, and not on the stereogenic centres of the 1,4-dioxane backbone.

1. Introduction

Carbon–carbon bond formation reactions are amongst the most useful in organic chemistry, because they allow the assembly of the carbon skeleton of a molecule from smaller fragments. For this purpose, the conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is one of the most widely used methods. The possibility of creating a stereogenic centre during this process has led to the development of methods that employ chiral auxiliaries or chirally modified nucleophiles, particularly organometallic reagents, that is, organolithium, Grignard and organozinc reagents, or chiral organocopper compounds in which the chiral ligand is non-transferable and controls the stereochemical course of the reaction. More powerful methods are those that employ a catalytic amount of both metal and chiral ligand, an area of research that has been intensively covered over the last few years, and has been the subject of several reviews.[1] A few metals have been used for this process, but copper-catalyzed enantioselective Michael additions remain the most widely used, combined with binaphthalene-, TADDOL- and oxazoline-derived ligands. We are interested in using inexpensive and readily available biomass-derived materials as chiral sources for the synthesis of, among other things, chiral ligands. During the course of this work, we developed some novel bis(oxazoline) ligands derived from (*R*,*R*)-(+)-tartaric acid with a 1,4-dioxane skeleton,[2,3] and were interested in testing their potential in catalyzing Michael addition reactions. Chiral oxazoline ligands were first used in catalytic enantioselective Michael additions in 1993 by Zhou and Pfaltz[4] who found an oxazoline thiophenolate that gave enantiomeric excesses of up to 87% in addition reactions to cyclic enones. Since then, other mono-oxazoline ligands have been tested in this reaction, namely aryl-substituted and phenylthio-substituted oxazolines,[5] ferrocenyl phosphine oxazolines,[6] BINOL oxazoline phosphites[7] and aminophosphine-oxazolines.[8] Pfaltz's oxazoline phosphites[7] have proven to be very versatile, giving high ee values with a wide range of substrates, simply with small variations in the substitution pattern of the ligands. Sammakia's ferrocenyl phosphine oxazoline[6] is one of the few ligands in this area that gives equally high enantiomeric excesses with cyclic enones and an acyclic one, namely benzalacetone. Generally, these reactions show very high ligand–substrate specificity. This factor, combined with a lack of theoretical means to predict which is the best ligand for a particular situation, is indeed a characteristic of many

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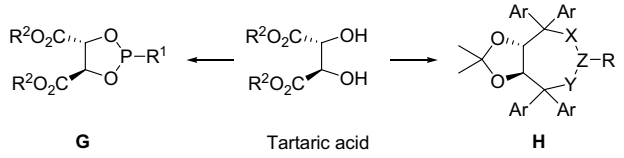
metal-catalyzed enantioselective reactions and is one of the reasons why there is a continuing need for more research in this area.[1]

Chiral bis(oxazoline) ligands have also found wide application in catalytic Michael addition reactions as shown in Figure 1.[9–13] Bis-triflate or bis-hexafluoroantimonate copper(II) complex A, originally developed by Evans et al.[14] for Diels–Alder reactions, gives high enantiomeric excesses in numerous applications. Tartaric acid has provided the chiral framework of many ligands in this area. Derivatization of the hydroxyl groups produces cyclic phosphites of type G[4,16] (Scheme 1), and derivatization of the carboxyl groups produces TADDOLs[17] of type H used as O/S or N/S copper chelates (H: X, Y = O, N, S and Z = Cu),[18] or as phosphites,[19] amidites[20] or phosphinates.[18,20] Generally, they induce low to moderate enantioselectivity unless there is exocyclic chirality.[1a] For instance, with an exocyclic chiral alcohol[18] (H: X, Y = O, Z = P, R = (1*S*,2*R*)-Ph-cyclohexanol) 96% ee was obtained with cyclohexenone. Interestingly, its diastereoisomer provided no induction, giving a good example of a strong match–mismatch effect.



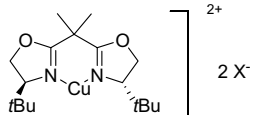
Scheme 1.

We decided to test our tartrate-derived ligands in the addition of diethylzinc to enones. This reaction has received considerable attention with many ligands, because these reagents have high functional group tolerance, lower basicity than many organometallic reagents, and in the presence of TMSCl as an additive, or a metal catalyst, that is, Cu, Co, Ni, what is otherwise a sluggish reaction, may be converted into a highly efficient process. Bis(oxazolines) D–F (Fig. 1) were already tested by Reiser et al.[13] in this reaction, and the enantiomeric excess obtained was found to be very dependent on the ligand structure. They found, for instance that although ligand D gave excellent induction in many reactions, in the Michael addition the products were racemic. With bis(oxazolines) E–F, enantioselectivities varied between 0% and 94% ee. Herein, we report the synthesis of novel inexpensive tartrate-derived bis(oxazoline) ligands and the results of our studies on the copper-catalyzed enantioselective Michael addition of diethylzinc to enones.

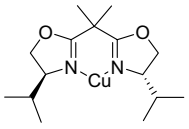
2. Results and discussion

2.1. Synthesis of bis(oxazolines)

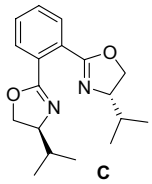
Chiral oxazolines are normally prepared from commercially available enantiomerically pure α-amino acids or amino alcohols obtained by reduction.[21] The method used in this work involved a synthetic route in which initially the cyclic diacetal diester was condensed with the corresponding 1,2-amino alcohols to form the bis(hydroxy)amide derivatives.[2a,22] Subsequently, the hydroxyl groups in the bis(hydroxy)amides were activated as mesylates, which were isolated and treated with base (NaOH) to produce the cyclic bis(oxazolines). Later we found that by using *p*-toluenesulfonyl chloride in the presence of a large excess of base (Et_3N), the activation and cyclization occur in one-pot, to produce the bis(oxazolines) directly in equal or better yields and



A: X = TfO, SbF



B



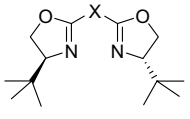
C

Scolastico,[9] Mukaiyama-Michael addition of silyl ketene acetals to 2-methoxy-carbinylcyclo-2-en-1-one

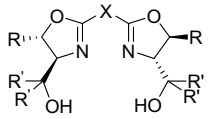
Katsuki,[10] Addition of (trimethylsilyloxy)furans to oxazolidinone enolates.

Evans,[11] Mukaiyama-Michael additions to alkylidene malonates and fumaryl oxazolidinones

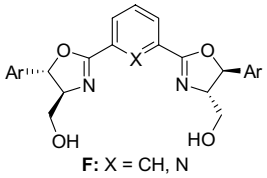
Takamoto,[12] Addition of Me_3Al to cyclic dienones



D: X = CMe_2, NH



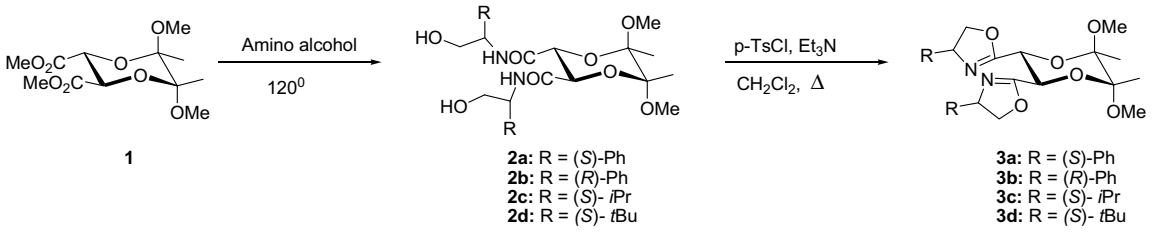
E: X = CH_2, $(CH_2)_2$, CMe_2



F: X = CH, N

Reiser,[13] Diethylzinc addition to enones

Figure 1. Bis(oxazoline) ligands used in copper-catalyzed conjugate addition reactions.



Scheme 2. Synthesis of bis(oxazolines).

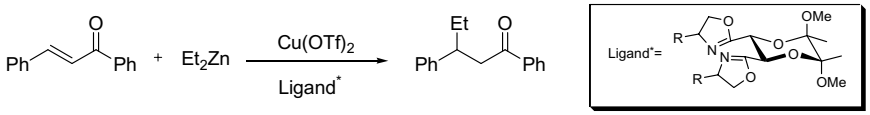
cleanly, as evidenced by ^{1}H NMR spectroscopy (Scheme 2). This method has already been used by us in the preparation of oxazoline carbinols.[3a,23] The process is very suitable to the acid-sensitive diacetal substrate. The bis(oxazolines) were stable for several weeks in the refrigerator, but degraded within days when left to stand at room temperature. They were found to be quite sensitive to acid, even to traces of acid in deuterated chloroform, and they had to be chromatographed rapidly on silica gel, which may account for the moderate to good yields obtained.

2.2. Catalytic reactions: the addition of diethylzinc to chalcone

To test the ability of the new ligands to induce chirality in the addition of diethylzinc to enones, chalcone and 2-cyclohexenone were chosen as model substrates, representative of an acyclic and a cyclic enone, respectively. $Cu(OTf)_2$ was chosen as the copper catalyst. It is known that both Cu I and Cu II copper salts catalyze the addition reaction successfully, with similar catalytic activities, but Cu(II) triflate is often better and is also more convenient to use because Cu I is very sensitive to oxidation. Typical reaction conditions were chosen to start: an excess of Et_2Zn to substrate of 1.5–1, 3 mol % of Cu catalyst and a ligand to metal ratio of 2:1. Preliminary experiments showed that approx. 17 h at 0 °C were needed for complete conversion of the starting material. At −15 °C, the reaction was slower, and only one third of the chalcone had reacted within this time period. Toluene was found to be the best solvent, and the product of the 1,4-addition was obtained in 46% ee under these conditions, using $Cu(OTf)_2$–**3a** as catalyst. In CH_2Cl_2, the ee was lower (14%), in THF a more complex mixture was obtained although the enantiomeric excess was 35% with a reversal of stereochemistry also being observed (the (*R*)-enantiomer formed vs the (*S*)- in toluene). In MeCN the reaction was even more sluggish. In toluene, an increase in the mole ratio of the catalyst from 3 to 6 mol % had practically no effect on the stereochemical outcome of the reaction (47% ee was obtained). However, the reaction was more chemoselective, and the yield of the 1,4-addition product went up from 31% to 50%. Using the optimized reaction conditions, each of the new bis(oxazolines) were tried as a possible chiral ligand. The results are shown in Table 1. The reactions afforded a mixture of products, with the isolated yield of the 1,3-diphenylpentanone usually below 50%. The best catalyst was $Cu(OTf)_2$–**3a**, which gave both the best enantioinduction (entries 1 and 2), as well as the highest yield (50%). Not only the structure of the ligand but also the configuration of the stereogenic centre on the oxazoline ring had an important influence on the results, since diastereomeric ligands **3a** and **3b**, which had an opposite configuration at the oxazoline stereogenic centre, produced a dramatic difference (Δee = 43%).

The addition reaction was also attempted with the reaction conditions described above and $Ni(acac)_2$–**3a** as catalyst, in CH_2Cl_2. The reaction was chemoselective, but racemic 1,3-diphenylpentanone was obtained as the major product (52%).

Table 1. Effect of the ligand substitution pattern on the enantioselective addition of diethylzinc to chalcone catalyzed by $Cu(OTf)_2$:chiral bis(oxazoline)[a]



Entry	Ligand	R	Mol % Cu	ee[c] (%)	Configuration
1	**3a**	(S)-Ph	3	46	*S*
2[b]	**3a**	(*S*)-Ph	6	47	*S*
3	**3b**	(*R*)-Ph	3	3	*R*
4	**3c**	(*S*)-*i*Pr	3	31	*S*
5	**3d**	(*S*)-*t*Bu	3	31	*S*

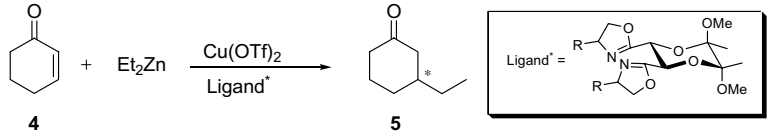
[a] All reactions were carried out under argon, in toluene, with [chalcone] = 0.2 M and chalcone:Et_2Zn:$Cu(OTf)_2$:Ligand = 1:1.5:0.03:0.06, except entry 2.
[b] Cu:Ligand 6:12 mol %.
[c] Determined by HPLC analysis on a chiral column (Chiralcel OD-H).[24]

2.3. The addition of diethylzinc to 2-cyclohexenone

For the cyclic enone, the reactions were chemoselective, producing the desired 1,4-addition product exclusively, as observed by ^{1}H NMR spectroscopy. The effects of the temperature and nature of the solvent on the enantioselectivity of the reaction were investigated first (Table 2) using typical reaction conditions and Cu(OTf)$_2$–**3c** as catalyst. It was found once again that the outcome was strongly dependent on the nature of the solvent. Similar results (Δee = 4%) could be obtained in CH_2Cl_2 and toluene (31% and 35% ee, respectively), but MeCN was highly detrimental to the stereochemical outcome of the reaction, giving an almost racemic product (4% ee), with a reversal in the sense of asymmetric induction, but full conversion, within the same time period. The effect of the solvent on the outcome of the conjugate addition reactions described above follows the general trend observed by other researchers that in copper-catalyzed reactions coordinating solvents are unfavourable either to the yield of product, or to its enantiomeric purity, or to both.[2] When all the other variables were kept constant and the temperature was dropped from 0 to −50 °C, it was found that the enantiomeric excess increased as the temperature was lowered, with the best result being obtained at −20 °C (42% ee). Lowering the temperature further was detrimental to the enantioselectivity. At −50 °C, the reaction was slowed down to the point that after 17 h there remained 15% 2-cyclohexenone in the crude reaction mixture, as determined by ^{1}H NMR spectroscopy. Although when toluene was used as solvent, the enantiomeric excess was slightly higher than with CH_2Cl_2, the difference was small (Δee = 4%), and thus CH_2Cl_2 was chosen as solvent for the next set of experiments, due to its higher volatility. The boiling point difference between toluene and the starting material and product of the reaction is smaller, which makes product isolation during solvent evaporation more difficult.

The effect of structural variations of the ligand on the reaction was then investigated with the optimized reaction conditions. Timed experiments, monitored by ^{1}H NMR spectroscopy, were used to establish the length of time required for full conversion of the substrate under these conditions. It was established that after 3 h, there was full conversion of the substrate. The reaction was repeated afterwards with each of the new bis(oxazolines) as chiral ligands. The results are presented in Table 3. In each case, there was full conversion of the starting material, and the reaction was chemoselective, as determined by ^{1}H NMR spectroscopy. The results show that the enantiomeric excess obtained, as expected, is very dependent on the structure of the chiral ligand. It varied between 20% and 50%. When a 2:1 ratio of ligand to metal was used, the highest ee value was obtained with **3a** or **3d** (49% and 50%, respectively). The results also show that the configuration of the stereogenic centre on the oxazoline ring determines the configuration of the product, but not the stereogenic centres of the dioxane ring, since **3a** and **3b** gave products of opposite configuration. This is also a good example of a strong match–mismatch effect, since when the configuration of the stereogenic centre on the oxazoline ring is varied and the configuration of the stereogenic centres on the dioxane ring remains the same, Δee = 29%, as observed in the reactions with **3a** and **3b** (entries 1 and 2, Table 3) and also with the acyclic substrate (Table 1, entries 1–3). This conjugate addition reaction was also tried in the presence of molecular sieves. It has been found in some cases,[2] but not always, that the addition of powdered molecular sieves to the reaction mixture has a beneficial effect on enantioselectivity. This is thought to be either due to the presence of traces of water, or as a result of physical adsorption to the surface of the sieves. Cu(OTf)$_2$–**3a** was used as catalyst in combination with sieves, but there was no significant change in the result (Table 3, entry 7). In an attempt to improve the enantiomeric excess, the ratio of the ligand to metal was also varied since different catalytic complexes may also form. In these cases, the improvement in ee was also very small: Δee = +5, entries 7 and 8 (Table 2) and Δee = +4, entries 1 and 8 (Table 3). Increasing the concentration of catalyst from 3 to 6 mol % also caused only a very small increase (Δee = +3).

Table 2. Effect of solvent and temperature on the enantioselective 1,4-addition of diethylzinc to cyclohex-2-enone catalyzed by Cu(OTf)$_2$–ligand **3c**[a]

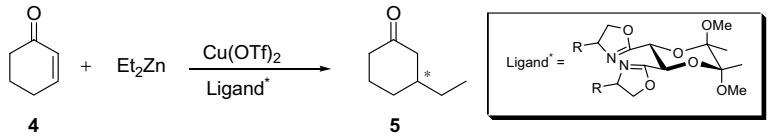


4 **5**

Entry	Ligand:Cu	Solvent	Temperature (°C)	ee[b] (%)	Configuration
1	2:1	CH_2Cl_2	0	31	*S*
2	2:1	MeCN	0	4	*R*
3	2:1	Toluene	0	35	*S*
4	2:1	Toluene	−20	42	*S*
5	2:1	Toluene	−40	39	*S*
6	2:1	Toluene	−50	26	*S*
7	2:1	Toluene/CH_2Cl_2	−20	33	*S*
8	3:1	Toluene/CH_2Cl_2	−20	38	*S*

[a] All reactions were carried out using [cyclohexenone] = 0.2 M, Cu(OTf)$_2$ = 3 mol %, cyclohexenone:Et$_2$Zn 1:1.3–1.5, reaction time = 17 h.
[b] Determined by ^{13}C NMR analysis of the cyclic aminal derived from the reaction with (*R*,*R*)-1,2-diphenylethylene diamine.[25]

Table 3. Effect of ligand structure, configuration and concentration on the enantioselective conjugate addition of diethylzinc to cyclohex-2-enone catalyzed by $Cu(OTf)_2$–chiral bis(oxazolines) **3a–d**[a]



4 **5**

Entry	Ligand	R	Solvent	Mol % Cu	Ligand:Cu	Conv.[b] (%)	ee[c] (%)	Config.[d]
1	**3a**	(*S*)-Ph	CH_2Cl_2	3	2:1	100	49	*S*
2	**3b**	(*R*)-Ph	CH_2Cl_2	3	2:1	100	20	*R*
3	**3c**	(*S*)-*i*Pr	Toluene	3	2:1	100	42	*S*
4	**3d**	(*S*)-*t*Bu	CH_2Cl_2	3	2:1	100	50	*S*
5	**3a**	(*S*)-Ph	CH_2Cl_2	6	2:1	100	52	*S*
6[e]	**3a**	(*S*)-Ph	Toluene	6	2:1	100	45	*S*
7[f]	**3a**	(*S*)-Ph	CH_2Cl_2	3	2:1	100	50	*S*
8	**3a**	(*S*)-Ph	CH_2Cl_2	3	4:1	100	53	*S*

[a] All reactions were carried out using [cyclohexenone] = 0.4 M, and cyclohexenone:Et_2Zn 1:1.4–1.6.
[b] The conversion was determined by analysis of the ^1H NMR spectra.
[c] Determined by ^{13}C NMR analysis, from the ratio of the diastereomeric cyclic aminals formed by reaction with (*R*,*R*)-1,2-diphenylethylenediamine.[25]
[d] The configuration was determined by ^{13}C NMR analysis, by comparison with the chemical shifts of published data.[25]
[e] [Cyclohexenone] = 0.3 M.
[f] Molecular sieves were added to the reaction mixture.

3. Conclusion

In conclusion, we have developed a methodology to synthesize novel chiral bis(oxazolines) derived from tartaric acid. Their potential to act as chiral ligands in metal-catalyzed reactions was tested on the copper-catalyzed addition of diethylzinc to an acyclic and a cyclic enone. Additions to the cyclic enone were generally less selective than to the cyclic one, probably due to s-*cis* and s-*trans* interconversion of the former. With these new ligands, the enantioinduction obtained with chalcone was similar to that obtained with 2-cyclohexenone, 50% and 53%, respectively, with **1a** the best ligand. However, only the reactions with the cyclic substrate produced the conjugate addition product exclusively. It was found that the ee obtained did not vary much with the concentration of the catalyst, or the catalyst to ligand ratio, but it was very dependent on the reaction conditions (solvent, temperature), and on structural variations in the ligand. A strong match–mismatch effect was found to occur between the dioxane moiety and the chiral centre in the oxazoline ligand. The results obtained are promising, and suggest that the ligands may be useful for other metal-catalyzed reactions.

4. Experimental

4.1. General methods

All reactions were carried out under an atmosphere of argon. Solvents were purified by standard procedures and distilled before use. Column chromatography was carried out on Mackerey-Nagel GmbH & Co silica gel (230–400 mesh). Melting points were measured on a Electrothermal Melting Point apparatus, and are uncorrected. Optical rotations (0.5 dm cell, 1 mL capacity) were measured on an AA-1000 Polarimeter from Optical Activity Ltd. NMR spectra were obtained on a Bruker AR X400 NMR spectrometer. Chemical shifts are reported relative to TMS. The DEPT sequence was used for multiplicity assignments of ^{13}C NMR spectra signals. Two-dimensional spectra (COSY 45, HMQC and SECSY) were recorded whenever necessary for structure elucidation. IR spectra were obtained on a Mattson Instruments Satellite FTIR spectrometer. Mass spectra were recorded on a Micromass GCT spectrometer, operating in the electron impact mode, and were supplied by the Mass Spectrometry Services of the Chemistry Department/REQUIMTE, FCT, UNL. Elemental analysis (C, H and N) was performed by the Laboratory for External Services of CQFB-Lab Associado/REQUIMTE, of the Department of Chemistry, FCT, UNL, Monte de Caparica. HPLC analysis was performed on a Merck Hitachi instrument equipped with a Chiralcel OD-H column, with hexane/*i*PrOH as eluent and a Merck-Hitachi-4250 UV–vis detector. Commercial DL-1-phenylethanol was used as reference standard.

4.2. General procedure for amidation

Diester **1** (1.0 mmol) and the amino alcohol (1.0 mmol) were mixed, heated up to 120 °C and stirred at this temperature, under argon, for 17 h. The remaining methanol was removed under high vacuum. The crude product was purified as described for each amide, or used as it is in the next step.

4.2.1. (2*R*,3*R*,5*R*,6*R*)-2,3-Bis[*N*-(1′*S*)-(1′-phenyl-2′-hydroxyethyl)-amido]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 2a. Prepared from diester **1** and (*S*)-phenylglycinol according to the general procedure for amidation. The product was purified by column chromatography on silica gel (acetone/CH_2Cl_2 2:3) to give a white solid (63%). Mp 55–56 °C; $[\alpha]_D^{23} = -12.0$ (*c* 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.34 (s, 6H, $2 \times CH_3$), 2.16 (d, $J = 6.4$ Hz,

2 × OH), 3.26 (s, 6H, 2 × OCH_3), 3.84 (m, 2H, 2 × C*H*HO), 4.01 (d, 2H, $J = 10.8$ Hz, 2 × CH*H*O), 4.43 (s, 2H, 2 × dioxane-CH), 5.10 (m, 2H, 2 × CHN), 7.03 (d, 2H, $J = 7.6$ Hz, 2 × NH), 7.28–7.38 (m, 10H, Ph–H) ppm; ^{13}C NMR ($CDCl_3$): δ 17.7 (2 × CH_3), 48.5 (2 × OCH_3), 55.6 (2 × CHN), 65.3 (2 × CH_2), 72.4 (2 × dioxane-CH), 100.0 (2 × acetal-C), 126.9 (4 × *m*-C, Ph), 127.9 (2 × *p*-C, Ph), 128.8 (4 × *o*-C, Ph), 138.7 (*i*-C, Ph), 167.9 (2 × C=O) ppm; IR ($CHCl_3$): *v* 3413, 3066, 3031, 3007, 2950, 2839, 1670, 1523, 1495, 1456, 1379, 1208, 1145, 1112, 1079, 1035, 928, 891, 761, 738, 701 cm^{-1}. MS (*m*/*z*, relative intensity): 502 (M^+, 0.01%), 453 (21), 165 (78), 159 (36), 152 (41), 201 (27), 200 (59), 198 (27), 197 (22), 187 (40), 186 (52), 132 (20), 121 (45), 120 (33), 117 (21), 116 (53), 115 (42), 106 (100), 105 (22), 104 (87), 103 (47), 101 (45), 91 (48), 89 (20), 77 (28), 73 (20). Anal. Calcd for $C_{26}H_{34}N_2O_8$ (502.56): C 62.14, H 6.82, N 5.57. Found: C 62.01, H 7.01, N 5.55.

4.2.2. (2*R*,3*R*,5*R*,6*R*)-2,3-Bis[*N*-(1′*R*)-(1′-phenyl-2′-hydroxyethyl)-amido]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 2b. Prepared from diester **1** and (*R*)-phenylglycinol according to the general procedure for amidation. The product was purified by column chromatography on silica gel (acetone/$CHCl_3$ 2:3) to give a white solid (47%). Mp 56–57 °C; $[\alpha]_D^{18} = -90.0$ (*c* 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 6H, 2 × CH_3), 3.21 (s, 6H, 2 × OCH_3), 3.38 (m, 2H, OH), 3.88 (m, 4H, 2 × CH_2), 4.43 (s, 2H, 2 × CH), 5.03 (m, 2H, 2 × CHN), 6.91 (d, 2H, $J = 7.6$ Hz, 2 × NH), 7.32 (m, 10H, 10 × Ph–H) ppm; ^{13}C NMR ($CDCl_3$): δ 17.7 (2 × CH_3), 48.6 (2 × OCH_3), 56.1 (2 × CHN), 65.3 (2 × CH_2), 70.8 (2 × CH), 99.5 (2 × acetal-C), 127.1 (4 × *m*-C, Ph), 127.9 (2 × *p*-C, Ph), 128.9 (4 × *o*-C, Ph), 138.9 (*i*-C, Ph), 168.6 (2 × C=O) ppm; IR ($CHCl_3$): *v* 3413, 3065, 3009, 2950, 2838, 1671, 1522, 1496, 1455, 1378, 1234, 1220, 1145, 1115, 1079, 1049, 1038, 932, 909, 891, 780–757, 740, 701, 665 cm^{-1}. MS (*m*/*z*, relative intensity): 503 (M+1, 0.01%), 502 (M^+, 0.05), 454 (20), 453 (23), 318 (89), 305 (48), 288 (42), 201 (29), 200 (72), 198 (28), 197 (42), 187 (34), 186 (44), 121 (42), 120 (31), 116 (45), 115 (39), 106 (100), 104 (85), 103 (45), 101 (37), 91 (46), 77 (26). Anal. Calcd for $C_{26}H_{34}N_2O_8 \cdot H_2O$ (520.58): C 59.99, H 6.97, N 5.38. Found: C 60.34, H 6.77, N 5.38.

4.2.3. (2*R*,3*R*,5*R*,6*R*)-2,3-Bis[*N*-(1′*S*)-(1′-isopropyl-2′-hydroxyethyl)-amido]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 2c. Prepared from diester **1** and (*S*)-valinol according to the general procedure for amidation. Purified by column chromatography on silica gel (acetone/$CHCl_3$ 1:1) to give a very hygroscopic solid (67%); $[\alpha]_D^{20} = -86.0$ (c 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.96 (app. t, 12H, $J = 7.6$ Hz, 4 × CH_3 of *i*Pr), 1.35 (s, 6H, 2 × CH_3), 1.90 (m, 2H, 2 × CH of *i*Pr), 3.27 (s, 6H, 2 × OCH_3), 3.60–3.70 (m, 4H, 2 × CHN+2 × C*H*HO), 3.80 (d, 2H, $J = 10.8$ Hz, 2 × CH*H*O), 4.35 (s, 2H, 2 × dioxane-CH), 6.51 (d, $J = 8.4$ Hz, 2 × NH) ppm; ^{13}C NMR ($CDCl_3$): δ 18.1 (CH_3), 19.4 (CH_3), 20.0 (CH_3), 29.3 (CH of *i*Pr), 48.8 (2 × OCH_3), 57.8 (2 × CHN), 63.1 (2 × CH_2OH), 72.9 (2 × dioxane-CH), 100.3 (2 × acetal-C), 168.5 (2 × C=O) ppm; IR ($CHCl_3$): *v* 3413, 3006, 2965, 2877, 2838, 1666, 1530, 1466, 1379, 1334, 1218, 1144, 1113, 1077, 1048, 1037, 927, 906, 889, 664, 585 cm^{-1}. MS (*m*/*z*, relative intensity): 436 (M+2, 0.01%), 435 (0.06), 434 (0.24), 185 (14), 285 (12), 237 (29), 225 (12), 208 (10), 207 (100), 184 (10), 166 (36), 116 (24), 115 (16), 101 (16). Anal. Calcd for $C_{22}H_{42}N_2O_8$ (434.53): C 55.28, H 8.82, N 6.45. Found: C 55.10, H 8.94, N 6.55.

4.2.4. (2*R*,3*R*,5*R*,6*R*)-2,3-Bis[*N*-(1′*S*)-(1′-*tert*-butyl-2′-hydroxyethyl)-amido]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 2d. Prepared from diester **1** and (*S*)-*tert*-leucinol according to the general procedure for amidation. The product was purified by column chromatography (acetone/chloroform 2:3) to give a white crystalline solid (55%). Mp 227 °C; $[\alpha]_D^{22} = -70.7$ (c 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.96 (s, 9H, 3 × CH_3 of *t*Bu), 1.37 (s, 6H, 2 × CH_3), 3.28 (s, 6H, 2 × OCH_3), 3.56 (dd, 2H, $J = 8.0$, 10.8 Hz, 2 × C*H*HOH), 3.86 (m, 4H, 2 × CH*H*OH and 2 × CHN), 4.46 (s, 2H, 2 × dioxane-CH), 6.44 (d, 2H, $J = 9.2$ Hz, 2 × NH) ppm; ^{13}C NMR ($CDCl_3$): δ 17.9 (2 × CH_3), 26.8 (3 × CH_3 of *t*Bu), 33.3 (2 × Cq of *t*Bu), 48.5 (2 × OCH_3), 59.6 (2 × CHN), 62.2 (2 × CH_2), 72.4 (2 × dioxane-CH), 100.0 (2 × acetal-C), 168.6 (2 × C=O) ppm; IR ($CHCl_3$): *v* 3415, 3005, 2966, 2910, 2875, 2839, 1668, 1530, 1476, 1402, 1378, 1371, 1232, 1145, 1112, 1076, 1049, 929, 905, 888, 772, 762, 740, 665, 602, 428 cm^{-1}. MS (*m*/*z*, relative intensity): 462 (M^+, 2%), 433 (16), 432 (75), 431 (13), 399 (17), 368 (10), 367 (10), 341 (20), 223 (10), 222 (68), 221 (100), 198 (16), 188 (12), 180 (11), 168 (13), 166 (10), 165 (37), 164 (14), 137 (12), 123 (10), 116 (35), 115 (20), 101 (30), 83 (10), 73 (13), 57 (27). Anal. Calcd for $C_{22}H_{42}N_2O_8$ (462.58): C 57.12, H 9.15, N 6.06. Found: C 57.26, H 9.44, N 6.27.

4.3. General procedure for bis(oxazoline) synthesis

The bisamide (1.0 mmol) was dissolved in dry dichloromethane (6.04 mL). Dry triethylamine (9.98 mL) and *p*-toluenesulfonyl chloride (2.26 mol) were added, and the solution was refluxed under argon for 17 h. The solution was cooled to room temperature and water (31 μL) was added. This was refluxed again for 40 min. Afterwards, it was cooled to rt and washed four times with water. The organic layer was dried through anhydrous sodium sulfate, and the crude product obtained after solvent evaporation on a rotary evaporator. Purification was carried out as described for each bis(oxazoline).

4.3.1. (2*R*,3*R*,5*R*,6*R*)-2,3-Bis[(4′*S*)-phenyloxazolin-2′-yl]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 3a. Prepared according to the general procedure for bis(oxazoline) synthesis. Purified by column chromatography on silica gel (CH_2Cl_2/EtOAc 4:1) to give a white solid (36% from diester **1**). Mp 132 °C; $[\alpha]_D^{21} = -151.4$ (*c* 1.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 6H, 2 × CH_3), 3.83 (s, 6H, 2 × OCH_3), 4.09 (app. t, 2H, $J = 8.4$ Hz, 2 × C*H*HO), 4.67 (app. t, 2H, $J = 10.0$ Hz, 2 × CH*H*O), 4.94 (s, 2H, 2 × dioxane-CH), 5.22 (app. t, 2H, $J = 10.0$ Hz, 2 × CHN), 7.22 (m, 10H, Ph–H) ppm; ^{13}C NMR ($CDCl_3$): δ 17.4 (2 × CH_3), 48.5 (2 × OCH_3),

65.7 (2 × dioxane-CH), 69.6 (2 × CHN), 74.8 (2 × CH_2O), 126.7 (4 × *m*-C, Ph), 127.5 (2 × *p*-C, Ph), 128.6 (4 × *o*-C, Ph), 141.5 (2 × *i*-C, Ph), 163.9 (2 × O–C=N) ppm. IR (CH_2Cl_2): *v* 3066, 3032, 2998, 2966, 2952, 2906, 2838, 1673, 1495, 1473, 1455, 1378, 1213, 1173, 1143, 1130, 1115, 1036, 985, 921, 905, 721, 544 cm^{-1}. MS (*m*/*z*, relative intensity): 466 (M^+, 0.03%), 435 (13), 319 (22), 318 (100), 317 (14), 289 (12), 288 (51), 214 (18), 198 (34), 197 (31), 183 (11), 182 (12), 171 (13), 143 (10), 120 (18), 117 (14), 116 (21), 115 (13), 105 (10), 104 (66), 103 (24), 101 (16), 91 (30), 90 (18), 89 (15). Anal. Calcd for $C_{26}H_{30}N_2O_6$ (466.53): C 66.94, H 6.48, N 6.01. Found: C 66.93, H 6.40, N 5.84.

4.3.2. (2*R*,3*R*,5*R*,6*R*)-2,3-Bis[(4′*R*)-phenyloxazolin-2′-yl]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 3b. Prepared according to the general procedure for bis(oxazoline) synthesis. Purified by column chromatography on silica gel (CH_2Cl_2/EtOAc 5:1) to give a white solid (45%). Mp 59–60 °C; $[\alpha]_D^{20} = -32.6$ (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.41 (s, 6H, 2 × CH_3), 3.38 (s, 6H, 2 × CH_3), 4.10 (t, 2H, $J = 8.8$ Hz, 2 × C*H*HO), 4.70 (t, 2H, $J = 8.4$ Hz, 2 × CH*H*O), 4.95 (s, 2H, 2 × CHN), 5.22 (t, 2H, $J = 9.6$ Hz, 2 × CHN), 7.23 (m, 10H, Ph–H) ppm; ^{13}C NMR ($CDCl_3$): δ 17.4 (2 × CH_3), 48.5 (2 × OCH_3), 65.6 (2 × dioxane-CH), 69.6 (2 × CHN), 75.0 (2 × CH_2), 99.2 (2 × acetal-C), 126.9 (4 × *m*-C, Ph), 128.8 (2 × *p*-C, Ph), 129.2 (4 × *o*-C, Ph), 141.5 (2 × *i*-C, Ph), 163.6 (2 × N=C–O) ppm. IR ($CHCl_3$): *v* 3028, 2998, 2968, 2907, 2838, 1673, 1603, 1495, 1473, 1455, 1379, 1367, 1244, 1143, 1131, 1114, 1034, 983, 923, 903, 860, 817, 700, 664 cm^{-1}. MS (*m*/*z*, relative intensity): 467 (M+1, 1%), 466 (M^+, 5), 451 (0.21), 319 (15), 318 (100), 288 (40), 214 (12), 198 (22), 197 (21), 120 (10), 116 (11), 104 (43), 103 (12), 91 (17). Anal. Calcd for $C_{26}H_{30}N_2O_6$ (466.53): C 66.94, H 6.48, N 6.01. Found: C 66.74, H 6.36, N 5.78.

4.3.3. (2*R*,3*R*,5*R*,6*R*)-2,3-Bis[(4′*S*)-isopropyloxazolin-2′-yl]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 3c. Prepared according to the general procedure for bis(oxazoline) synthesis. Purified by column chromatography on silica gel (CH_2Cl_2/EtOAc 4:1) to give a product, which at rt is a viscous liquid (44% from the diester, when the crude amide is used); $[\alpha]_D^{18} = -130.4$ (c 0.43, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.84 (d, 6H, $J = 6.8$ Hz, CH_3 of 2 × *i*Pr), 0.94 (d, 6H, $J = 6.8$ Hz, CH_3 of 2 × *i*Pr), 1.36 (s, 6H, 2 × CH_3), 1.68–1.76 (m, 2H, 2 × CH of *i*Pr), 3.34 (s, 6H, 2 × OCH_3), 3.90 (dd, 2H, $J = 6.8$, 9.6 Hz, 2 × oxazoline-CH), 3.97 (t, 2H, $J = 8.0$ Hz, 2 × C*H*H of oxazoline), 4.25 (t, 2H, $J = 8.0$ Hz, 2 × CH*H* of oxazoline), 4.73 (s, 2H, 2 × dioxane-CH); ^{13}C NMR ($CDCl_3$): δ 17.5 (2 × CH_3), 18.1 (CH_3 of 2 × *i*Pr), 19.1 (CH_3 of 2 × *i*Pr), 32.5 (2 × CH of *i*Pr), 48.4 (2 × OCH_3), 65.5 (2 × CH), 70.2 (2 × CH_2), 72.3 (2 × oxazoline-CH), 99.0 (2 × acetal-C), 162.3 (2 × O–C=N). IR ($CHCl_3$): *v* 2964, 2909, 2875, 2838, 1676, 1466, 1378, 1247, 1212, 1174, 1143, 1130, 1115, 1035, 985 cm^{-1}. MS (*m*/*z*, relative intensity): 398 (M^+, 0.01%), 397 (0.02), 367 (42), 250 (45), 208 (97), 207 (100), 179 (29), 164 (21), 163 (24), 153 (17), 152 (14), 120 (12), 115 (14), 101 (16), 42 (11). Anal. Calcd for $C_{20}H_{34}N_2O_6$ (398.50): C 60.28, H 8.60, N 7.03. Found: C 60.63, H 8.95, N 6.64.

4.3.4. (2*R*,3*R*,5*R*,6*R*)-2,3-Bis[(4′*S*)-*tert*-butyloxazolin-2′-yl]-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 3d. Prepared according to the general procedure for bis(oxazoline) synthesis. Purified by column chromatography on silica gel (CH_2Cl_2/EtOAc 7:3) to give a white solid (68% from the diester, when the crude amide is used). Mp 110–112 °C; $[\alpha]_D^{28} = -161.5$ (*c* 2.08, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.87 (t, 18H, 6 × CH_3 of *t*Bu), 1.35 (s, 6H, 2 × CH_3), 3.34 (s, 6H, 2 × CH_3), 3.85 (dd, $J = 8.0$, 10.0 Hz, 2 × CHN), 4.06 (appar. t, $J = 8.4$ Hz, 2 × C*H*HO), 4.16 (appar. t, $J = 8.4$ Hz, 2 × CH*H*O), 4.75 (s, 2H, 2 × CH); ^{13}C NMR ($CDCl_3$): δ 17.5 (2 × CH_3), 25.8 (6 × CH_3 of *t*Bu), 48.3 (2 × OCH_3), 65.6 (2 × CH), 68.7 (2 × CH_2), 75.6 (2 × CHN), 99.0 (2 × acetal-C), 162.0 (2 × O–C=N). IR ($CHCl_3$): *v* 2962, 2907, 2871, 2836, 1679, 1478, 1467, 1396, 1378, 1366, 1248, 1212, 1181, 1143, 1130, 1115, 1035, 984, 930, 905, 891, 861, 818, 769, 755, 744, 664, 553 cm^{-1}. MS (*m*/*z*, relative intensity): 396 (M^+−30, 1%), 395 (5), 379 (3), 337 (3), 295 (4), 278 (5), 223 (6), 222 (60), 221 (100), 220 (3), 219 (3), 202 (5), 180 (4), 168 (8), 167 (21), 166 (6), 165 (26), 164 (10), 163 (5), 162 (3), 137 (6), 135 (4), 123 (5), 122 (4), 121 (4), 116 (8), 115 (3), 83 (3), 57 (10). Anal. Calcd for $C_{22}H_{38}N_2O_6{\cdot}H_2O$ (444.57): C 59.44, H 9.07, N 6.30. Found: C 59.26, H 8.68, N 5.96.

4.4. General procedure for the asymmetric conjugate addition of diethylzinc to chalcone

Copper triflate (0.3 mmol), chiral ligand (0.6 mmol) and toluene (1.5 mL) were mixed and heated up to 51 °C for 45 min, under argon. Chalcone (0.10 g, 0.490 mmol) dissolved in toluene (0.3 mL) was then added dropwise, and the mixture stirred at room temperature for 10 min. The solution was then deaerated by freeze–pump–thaw, the reaction flask was filled with argon and cooled to 0 °C. Diethylzinc (0.75 mL of a 1.0 M solution in hexanes, 0.75 mmol) was added dropwise, and the reaction mixture was stirred at 0 °C for 17–20 h in a cryostat. The reaction was quenched with a 1 M HCl solution, and the product was extracted four times with EtOAc. After solvent removal on a rotary evaporator, the product was obtained as a solid, which was purified by preparative chromatography on silica gel (EtOAc/hexane 1:5). The enantiomeric excess was determined by HPLC, on a Chiralcel-OD column.

4.5. General procedure for the asymmetric conjugate addition of diethylzinc to 2-cyclohexenone

Copper triflate (0.045 mmol), chiral ligand (0.09 mmol) and dichloromethane (4.5 mL) were mixed and stirred at room temperature, under argon, for 30 min. The enone (0.15 mL, 1.5 mmol) was then added, and the mixture stirred at room temperature for 10 min. The solution was then deaerated by freeze–pump–thaw, the reaction flask was filled with argon and cooled to −20 °C. Diethylzinc (2.25 mL of a 1.0 M solution in hexanes, 2.25 mmol) was added dropwise, and the reaction mixture stirred at −20 °C for 3 h in a cryostat. The reaction was quenched with a 1 M HCl solution, and the product was extracted four times with dichloromethane. After solvent removal on a rotary evaporator, the

product was obtained as a clear liquid, still mixed with some dichloromethane. This was purified by preparative chromatography on silica gel (EtOAc/hexane 1:5). The enantiomeric excess was determined by ^{13}C NMR spectroscopy, from the ratio of the diastereomeric cyclic aminals produced after reaction with (*R*,*R*)-1,2-diphenylethylenediamine.[25]

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References

1. (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236; (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, *2*, 171–196; (c) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000, pp 569–592.
2. (a) Barros, M. T.; Burke, A. J.; Maycock, C. D.; Santos, C. R. In *Asymmetric Catalysis Using New Bis-oxazoline Ligands*, Tenth IUPAC symposium on organometallic chemistry directed towards organic synthesis, Versailles, France, 1999; (b) Barros, M. T.; Maycock, C. D.; Faisca Phillips, A. M. In *Novel chiral oxazoline carbinols and bis-oxazolines: synthesis and application in catalysis*, 5^0 Encontro Nacional de Química Orgânica e 1^0 Simpósio Luso—Japonês, Aveiro, Portugal, 2003; (c) For a recent review see: Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, D. J.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53–80.
3. For other applications of ligands with a 1,2-diacetal backbone in enantioselective catalysis see: (a) Barros, M. T.; Maycock, C. D.; Faisca Phillips, A. M. *Eur. J. Org. Chem.* **2004**, *8*, 1820–1829; (b) Li, W.; Waldkirk, X.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 7618–7623; (c) Haag, D.; Runsink, J.; Scharf, H. D. *Organometallics* **1998**, *17*, 398–409; (d) Berens, U.; Selke, R. *Tetrahedron: Asymmetry* **1996**, *7*, 2055–2064.
4. (a) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron Lett.* **1993**, *34*, 7725–7728; (b) Zhou, Q. L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467–4479.
5. Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Iwata, C. *Tetrahedron: Asymmetry* **1996**, *7*, 993–996.
6. Stangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503–16510.
7. (a) Knoebel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429–1431; (b) Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879–2888.
8. Blanc, C.; Agbossou-Niedercorn, F. *Tetrahedron: Asymmetry* **2004**, *15*, 757–761.
9. Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921.
10. Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015–17028.
11. (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994; (b) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865–868; (c) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595–598.
12. Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Aoe, K.; Hiramatsu, H.; Iwata, C. *Tetrahedron* **1996**, *52*, 14177–14188.
13. Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, *3*, 4259–4262.
14. (a) Evans, D. A.; Chapman, K. T.; Bisahay, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256; (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335.
15. Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3193–3196, see also Ref. 4.
16. For a recent review on TADDOLs see: Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92–138.
17. Seebach, D.; Jaeschke, G.; Pichota, A.; Audergon, L. *Helv. Chim. Acta* **1997**, *80*, 2515.
18. Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Leveque, J.-M.; Maze, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011–4027.
19. (a) Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1998**, *9*, 2409–2413; (b) Mandoli, A.; Arnold, L. A.; de Vries, A. H. M.; Savadori, P.; Feringa, B. L. *Tetrahedron: Asymmetry* **2001**, *12*, 1929–1937, see also Ref. 15.
20. (a) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579–2581; (b) Martorell, A.; Naasz, R.; Feringa, B. L.; Pringle, P. G. *Tetrahedron: Asymmetry* **2001**, *12*, 2497–2499.
21. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.
22. Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.
23. (a) Giordano, C.; Caviocchioli, S.; Levi, S.; Villa, M. *Tetrahedron Lett.* **1988**, *29*, 5561–5564; (b) Peer, M.; De Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547–7583.
24. See for instance: Bolm, C. *Tetrahedron: Asymmetry* **1991**, *2*, 701–704.
25. Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431–2434.