Synthesis of Chiral Amino Alcohols Embodying the Bispidine Framework and Their Application as Ligands in Enantioselectively Catalyzed Additions to C=O and C=C Groups

Jan Spieler,[a] Oliver Huttenloch[a] and Herbert Waldmann*[a]

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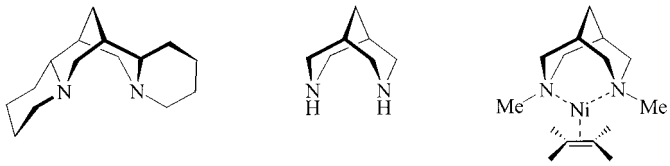
Two generally applicable routes for the synthesis of chiral amino alcohols embodying the bispidine framework have been developed. In linear route A the bispidine framework is built up successively from chiral primary amines via intermediate formation of a piperidinone and a bispidinone. In convergent route B an achiral bispidine is formed first and then the *N*-substituents are introduced by reaction of the nitrogen bases with chiral electrophiles. In order to determine if the bispidine core and its *N*-substituents can influence the steric course of enantioselective transformations, bispidine amino alcohols built up by these two routes were investigated as chiral ligands in the enantioselectively catalyzed addition of diethylzinc to aldehydes and chalcone. In general, tridentate ligands containing one chiral amino alcohol fragment and a second amino substituent without a stereogenic center were more efficient than tetradentate ligands with two amino alcohol structural units. With the best ligands the enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes proceeded with 83−98% *ee* and the nickel-catalyzed addition of diethylzinc to chalcone was achieved with up to 85% *ee*.

Introduction

The development of new ligands for the steric steering of enantioselective metal-catalyzed reactions is of great interest in organic synthesis.[1] In particular, nitrogen ligands have recently gained increasing importance.[2] They are often readily accessible from the "chiral pool", e.g. from amino acids and alkaloids, and their metal-coordinating properties can be fine-tuned by varying the hybridization and substitution of the nitrogen atoms.

In particular, the alkaloid sparteine **1** (Scheme 1) was introduced as an efficient ligand for enantioselective deprotonations,[3] for the steric steering of Pd-catalyzed allylation reactions[4] and the addition of organolithium compounds to imines.[5] The central structural core of sparteine **1** is bispidine **2**. This bicyclic nitrogen heterocycle is accessible by different methods,[6][7] opening up the opportunity to vary the ligand properties of bispidines by introduction of appropriate chiral substituents. Furthermore, Stetter et al.[6d] have demonstrated that unsubstituted bispidine **2** forms complexes with Ni^{II} and Cu^{II},[6a] and recently Pörschke et al. found that the bispidine−Ni^0 complex **3** is surprisingly stable.[8] The first bispidine carrying an *N*-alkyl substituent with a stereogenic center was synthesized by Beak et al.[3c] However, in asymmetric deprotonations it was less efficient than sparteine.

The ability of bispidines to form stable complexes with transition metals and the high levels of enantioselectivity induced by sparteine roused our interest in the synthesis of chiral bispidines and their investigation as ligands in enantioselective transformations. In this paper we describe two generally applicable methods for the synthesis of bispidines carrying hydroxyalkyl *N*-substituents with stereogenic centers and their preliminary investigation as mediators of enantioselectivity in two selected transformations. As model reactions the addition of diethylzinc to aldehydes and the Ni-catalyzed addition of diethylzinc to chalcone were chosen since both are well-established transformations for investigating the performance of chiral amino alcohols.[9][10]



1 **2** **3**

Scheme 1. Bispidine (**2**) as substructure of (−)-sparteine (**1**)

Results and Discussion

To synthesize differently substituted chiral bispidine amino alcohols we pursued the two different routes shown in Scheme 2.

In linear route A, the bispidine skeleton is built up in successive transformations starting from chiral amines via piperidinones **6** and bispidinones **5** as intermediates. Depending on the amines used, different substitution patterns can be generated. However, the chirality is introduced at an early stage of the synthesis and has to be carried through the procedure for the construction of the bicyclic heterocycle. Also only a limited number of chiral amines is available. These disadvantages may be overcome by convergent route B. In this case a preformed bispidine (**2** or **8**) is *N*-alkylated

[a] Max-Planck-Institut für moleculare Physiologie
Otto-Hahn-Strasse 11, D-44227 Dortmund, Germany
Fax: (internat.) + 49-(0)231/133-2499
E-mail: herbert.waldmann@mpi-dortmund.mpg.de

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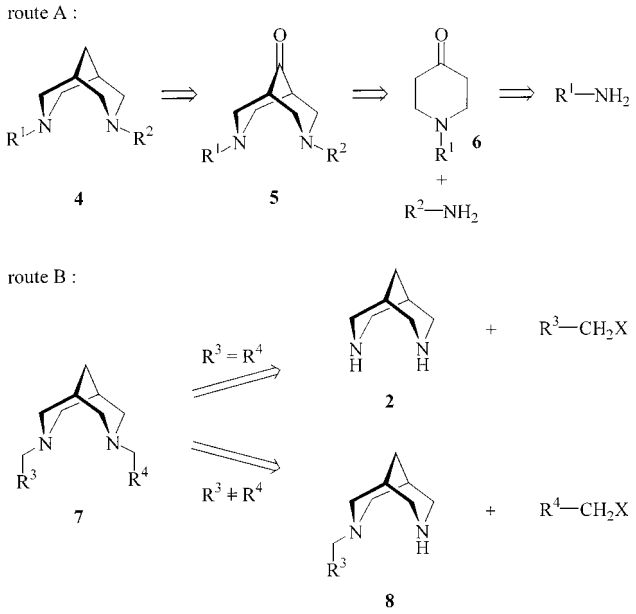
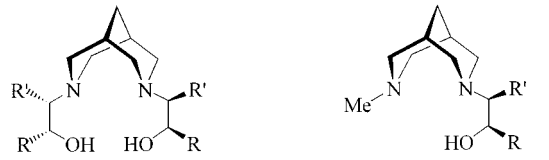


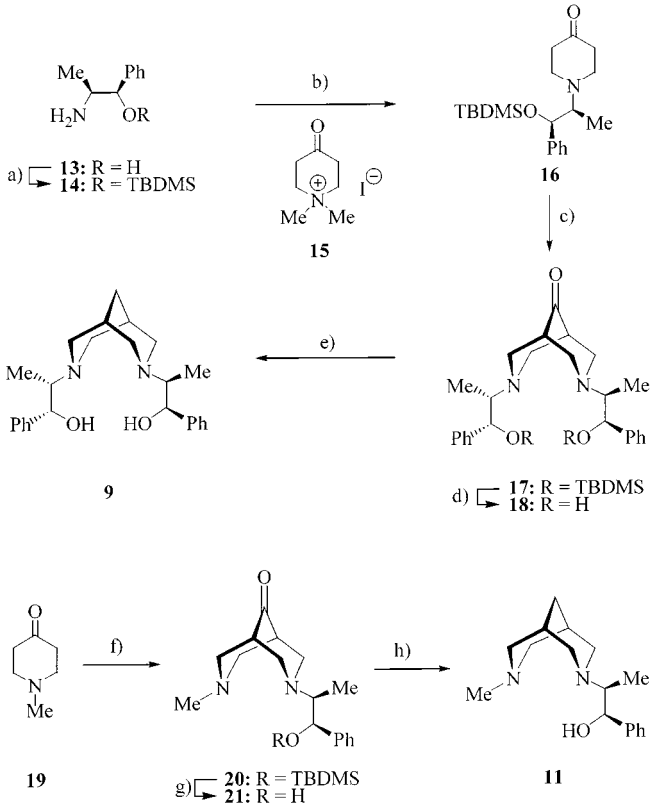
Scheme 2. Retrosynthetic analysis of the chiral substituted bispidines **2** and **8**

with a chiral electrophile. Thus, the chirality is introduced towards the end of the synthesis, i.e. after the heterocyclic framework has been built up. In addition, chiral electrophiles are readily available, e.g. alkyl halides, sulfonates and epoxides. By means of these strategies the model bispidine amino alcohols **9**−**12** (Scheme 3) were built up.



Scheme 3. Synthesized bispidine-derived amino alcohols

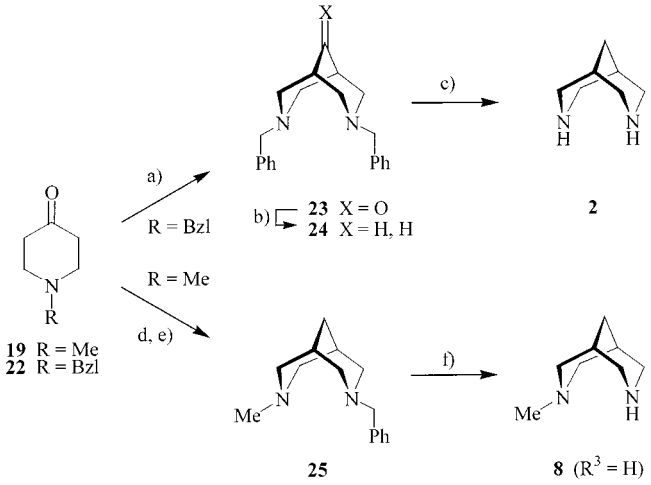
Bispidines **9** and **11**, embodying L-(−)-norephedrine **13**, were synthesized by linear route A (Scheme 4). To prevent undesired side reactions in the Mannich-type transformations used for the construction of the intermediary bispidinones, the amino alcohol **13** was *O*-silylated to give **14**.[11a] This ephedrine building block was treated with piperidinium iodide **15**[12] under basic conditions. In a sequential elimination/addition process norephedrine-derived piperidinone **16** was obtained in appreciable yield. Subsequent double Mannich reaction with formaldehyde and amine **14** yielded bispidinone **17**. This crucial transformation proceeded in only 39% yield due to formation of oligomers and polymers. The analogous Mannich reaction with *N*-methylpiperidinone **19** gave *N*-methylated bispidinone **20** with significantly higher yield. The introduction of two bulky TBDMS-protected substituents by this approach, therefore, appears to be only moderately efficient, possibly for steric reasons. *O*-Silylated bicyclic amino alcohols **17** and **20** were then deprotected and, finally, the ketones were deoxygenated to yield *N*,*N*′-disubstituted bispidines **9** and **11**. This final deoxygenation was accomplished in very high yield by means of a Wolff−Kishner reduction and proceeded without the formation of undesired by-products and epimerization. Amino alcohols **9** and **11** were isolated conveniently and in high purity by precipitation as hydrochlorides followed by liberation of the free nitrogen bases.



Scheme 4. Synthesis of the ligands **9** and **11** derived from L-(−)-norephedrine: (a) TBDMSCl, NEt_3, CH_2Cl_2, 93%; (b) **15**, K_2CO_3, EtOH, H_2O, 68%; (c) **14**, $(CH_2O)_n$, AcOH, MeOH, 39%; (d) TBAF, THF, 80%; (e) $N_2H_4 \cdot H_2O$, KOH, diethylene glycol, 75%; (f) **14**, $(CH_2O)_n$, AcOH, MeOH, 64%; (g) TBAF, THF, 86%; (h) $N_2H_4 \cdot H_2O$, KOH, diethylene glycol, 76%

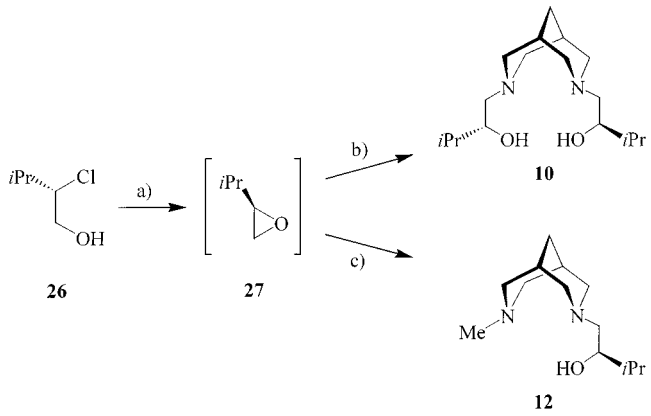
For the synthesis of amino alcohols **10** and **12** according to convergent route B, bispidines **2** and **8** were required. These heterocycles were synthesized by a modified version of the method reported by Smissman et al.[7] (Scheme 5). Double Mannich reaction of *N*-benzylpiperidinone **22** with formaldehyde and benzylamine yielded crystalline bispidinone **23** in 51% yield. After Wolff−Kishner reduction of the ketone the crude product was subjected to hydrogenolytic removal of the benzyl groups. Bispidine **2** was obtained in high yield by kugelrohr distillation. The crude product of the Mannich reaction between *N*-methylpiperidinone **19**, formaldehyde and benzylamine was directly subjected to Wolff−Kishner reduction. The resulting *N*-

methyl-*N*′-benzylbispidine **25** and also the debenzylated nitrogen base **8** were readily purified by distillation.



Scheme 5. Synthesis of the bispidines **2** and **8**: (a) Bzl−NH_2, $(CH_2O)_n$, AcOH, conc. HCl, MeOH, 52%; (b) KOH, $N_2H_4{\cdot}H_2O$, diethylene glycol, 94%; (c) H_2, Pd/C, AcOH, MeOH, 86%; (d) Bzl−NH_2, $(CH_2O)_n$, AcOH, conc. HCl, MeOH; (e) KOH, $N_2H_4{\cdot}H_2O$, diethylene glycol, 55% (after 2 steps); (f) H_2, Pd/C, AcOH, 85%

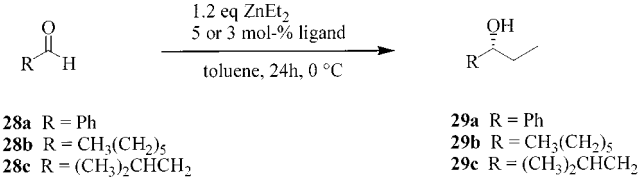
Finally, bispidines **2** and **8** were *N*-alkylated with chiral epoxide **27** to yield bispidine amino alcohols **10** and **12** in high yields (Scheme 6). Electrophile **27** was generated in situ from enantiomerically pure chlorohydrin **26**[13] by treatment with NaOMe in methanol.[14]



Scheme 6. Synthesis of the ligands **10** and **12** derived from the chiral epoxide **27**: (a) MeONa, MeOH; (b) **2**, MeOH, 74%; (c) **8**, MeOH, 73%

Both, the suitability of tri- and tetradentate bispidine-derived amino alcohols **9**−**12** as chiral ligands in metal-catalyzed asymmetric syntheses and the influence of the heterobicyclic system on such reactions were investigated by two representative transformations. It is well known that amino alcohols are efficient chiral ligands for the enantioselective addition of alkylzinc reagents to aldehydes.[9] They can also be used advantageously as mediators of chirality in the nickel-catalyzed conjugate addition of diethylzinc to enones.[10] Therefore, these two transformations were chosen as test reactions for bispidine-derived ligands **9**−**12**.

The addition of diethylzinc to some selected aldehydes **28a**−**c** (Scheme 7) was carried out in toluene by a standardized procedure (see Experimental Section). In this solvent the reaction proceeds only in the presence of a suitable ligand.[15] In the addition of the organometallic reagent to benzaldehyde, tetradentate ligand **9** gave respectable results. However, use of the analogous tridentate ligand **11** led to a much higher enantiomeric excess (98%) and the product was formed in nearly quantitative yield (Table 1, entries 1 and 2). A comparable result was observed when ligand **12** was employed (Table 1, entry 7). Similar *N*,*N*-dialkyl-substituted norephedrine and *N*-alkyl-substituted ephedrine ligands display somewhat lower *ee* values in this transformation.[9a][16] These results demonstrate that the presence of the bispidine system influences the efficiency of the stereoselection and, in particular, the second *N*-alkyl substituent appears to play an important role. The same trend was observed for addition of diethylzinc to two aliphatic aldehydes. For these reactions with other amino alcohols, in general, significantly lower enantioselectivity is observed. Ligand **11** yields both addition products with *ee* values of 83 and 85% in 94−95% yield, whereas the use of **9** leads to *ee* values and yields that are much lower (Table 1, entries 3−6). Tridentate ligand **12** is also clearly more efficient than tetradentate amino alcohol **9** (Table 1, entries 8 and 9).



Scheme 7. Asymmetric addition of diethylzinc to aromatic and aliphatic aldehydes **28** in the presence of bispidine-derived ligands

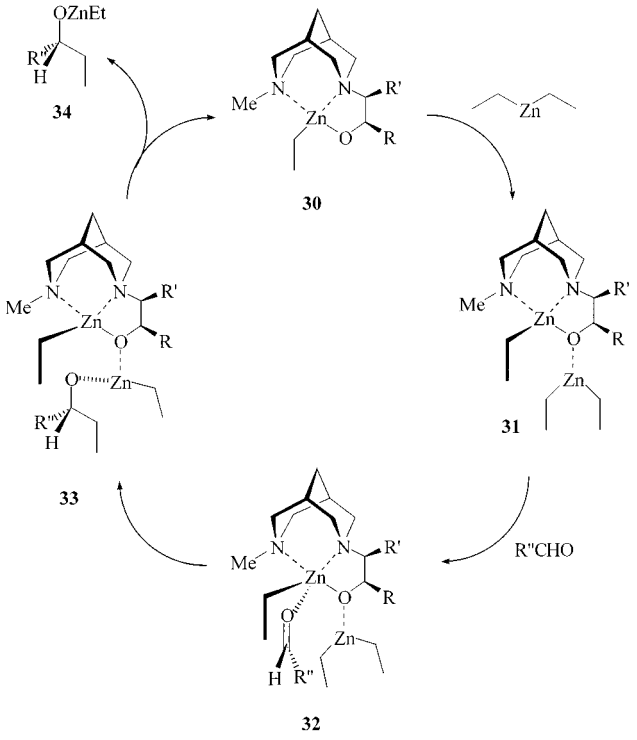
Table 1. Results of the asymmetric addition of diethylzinc to various aldehydes **28** in the presence of bispidine-derived ligands[a]

Entry	**28**, R =	Ligand	Yield [%][b]	*ee* [%][c]
1	Ph	**9**	72	85
2	Ph	**11**	96	98
3	$CH_3(CH_2)_5$	**9**	63	68[d]
4	$CH_3(CH_2)_5$	**11**	95	85[d]
5	$(CH_3)_2CHCH_2$	**9**	56	52[e]
6	$(CH_3)_2CHCH_2$	**11**	94	83[e]
7	Ph	**12**[f]	97	96
8	$CH_3(CH_2)_5$	**12**	92	77[d]
9	$(CH_3)_2CHCH_2$	**12**	91	79

[a] All reactions were carried out in toluene at 0 °C under argon for 24 h in the presense of 5 mol-% ligand unless otherwise indicated. − [b] Isolated yield after chromatography on silica gel. − [c] Determined by gas chromatographic analysis using a capillary column CS FS Cyclodex β-I/p. − [d] Determined using the acetate of **29b**. − [e] Determined using the trifluoroacetate of **29c**. − [f] 3 mol-% ligand was employed.

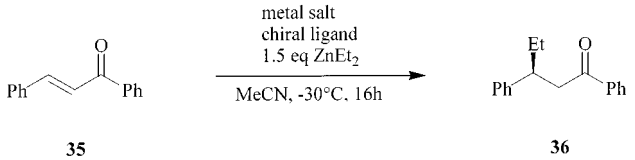
In all cases examined the (*R*) enantiomer of the secondary alcohol **29** was formed predominantly. This indicates that the stereochemical course of the transformation is the same, or at least very similar, for all bispidine ligands. This can be rationalized by analogy to the established model for

the enantioselectively catalyzed addition of dialkylzinc reagents to aldehydes in the presence of amino alcohols.[9] Accordingly, diethylzinc and the respective ligand would form complex **30**, which then serves as template for the coordination of a second zincalkyl opposite to residues R and R′ (**31**; Scheme 8). The aldehyde then also coordinates *anti* to these substituents of the amino alcohol group, with the sterically more demanding substituent R′′ pointing away from the bulky complex (**32**). Thereby, a six-membered transition state is passed in which the ethyl group is transferred to the *Re* side of the C=O group. This model implies that in the case of tetradentate ligand **9** only one of the two amino alcohol substructures is employed in complex formation. This is in accordance with the findings of Bolm et al.[9b] obtained for C_2-symmetric bipyridyl ligands in which also only one amino alcohol unit is involved in the steric steering of the asymmetric transformation. The observation that with tetradentate bis(amino alcohol) **9** the enantioselectivity was significantly lower than in the presence of *N*-methyl bispidine amino alcohol **11** also suggests that with **9**, additional complexes may be formed in which the stereoselection is less efficient.



Scheme 8. Possible mechanism for the addition of diethylzinc to aldehydes in the presence of bispidine-derived ligands

The trend in ligand efficiency observed in the addition of diethylzinc to aldehydes was also found in the Ni-catalyzed conjugate addition of diethylzinc to chalcone (Scheme 9, Table 2). In general, tridentate ligands **11** and **12** were superior to tetradentate amino alcohols **9** and **10**. Furthermore, ligand **11** was superior to bispidine derivative **12**, with respect to both enantioselectivity and yield. In the presence of ligands **9** and **10** only racemic product was obtained, indicating that with these bicyclic compounds no Ni complex was formed that could influence the steric course of the transformation.



Scheme 9. Asymmetric conjugate addition of diethylzinc to chalcone (**35**) in the presence of bispidine-derived ligands

Table 2. Results of the Ni^{II}-catalyzed asymmetric conjugate addition of diethylzinc to chalcone (**35**) in the presence of bispidine-derived ligands

Entry	Ligand [mol-%]	$Ni(acac)_2$ [mol-%]	Yield [%][a]	*ee* [%][b,c]
1	**12** (16)	7	69	53
2	**12** (20)	1	24	50
3	**12** (20)	1	76	70[d]
4	**12** (16)	7	33	45[e]
5	**11** (16)	7	92	79
6	**11** (20)	1	86	85[d]
7	**9** (13)	7	96	0
8	**10** (13)	7	95	0

[a] Isolated yield after chromatography on silica gel. – [b] Determined by HPLC using a DAICEL Chiracel OD. – [c] In each case **36** had the (*S*) configuration predominantly. – [d] 1 mol-% 2,2′-bipyridyl was added as coligand. – [e] Carried out at −50°C.

By analogy to observations made for other amino alcohols,[10] the *ee* value can be improved if the amount of Ni employed is reduced, more ligand is added and, additionally, 2,2-bipyridyl is used as a co-ligand at the same time (Table 2, entry 3). Lowering the temperature did not improve the enantioselectivity. In the best case, the desired chiral ketone was obtained in 86% yield with an enantiomeric excess of 85% (Table 2, entry 6). Recently, Feringa et al. reported that also with $Co(acac)_2$[17] and $ZnCl_2$[18] the addition of alkylzinc compounds to enones can be carried out enantioselectively. However, as shown in Table 3 (entry 1−4) in the presence of ligand **12** and in acetonitrile as solvent, Co, Cu and Zn salts are clearly less efficient than $Ni(acac)_2$. Furthermore, we observed a solvent-dependence of the enantioselectivity (entry 4−8) that parallels related findings published by Bolm et al.[10b] and Feringa et al.[10c][10d] Acetonitrile as solvent gives the best results, whereas in other solvents *ee* and yield are much lower. The use of propionitrile, which was found to be more advantageous than acetonitrile[10c][10d] in several cases, did not give better results in the presence of ligand **12** (Table 3, entry 6).

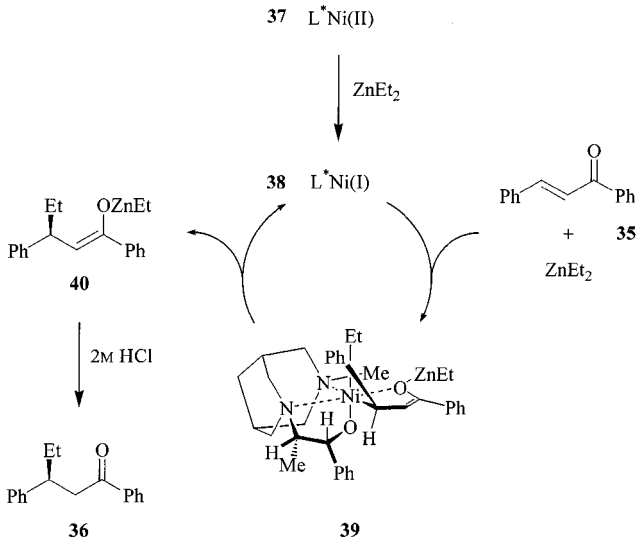
The reactions of diethylzinc with chalcone in the presence of the bispidine Ni complexes delivered predominantly the (*S*) enantiomer of the addition product. This can be rationalized on the basis of a mechanism proposed by Bolm et al.[10b] Presumably diethylzinc reacts with the Ni^{II} complex **37** to a catalytically active Ni^{I} species **38**. This complex then undergoes an electron transfer reaction to chalcone and a transmetallation with diethylzinc giving a Ni^{III} enolate complex **39** (Scheme 10). Reductive elimination finally leads to

Table 3. Results of the asymmetric addition of diethylzinc to chalcone (**35**) in the presence of zinc, cobalt and copper salts and different solvents[a]

Entry	Metal compound	Solvent	Yield [%][b]	*ee* [%][c,d]
1	$Co(acac)_2$	MeCN	13	6
2	$Cu(OTf)_2$	MeCN	39	0
3	$Zn(OTf)_2$	MeCN	–	–
4	$Ni(acac)_2$	MeCN	69	53
5	$Ni(acac)_2$	CH_2Cl_2	36	2
6	$Ni(acac)_2$	Propionitrile	47	48
7	$Ni(acac)_2$	THF	11	0
8	$Ni(acac)_2$	Toluene	61	11

[a] All reactions were carried out in the presence of 16 mol-% of ligand **12** and 7 mol-% of the metal salt according to the procedure described for $Ni(acac)_2$. – [b] Isolated yield after chromatography on silica gel. – [c] Determined by HPLC using a DAICEL Chiracel OD. – [d] Ketone **36** had the (*S*) configuration ketone predominantly.

formation of product enolate **40** and regeneration of the Ni^I intermediate **38**. The stereoselectivity observed if bispidine **11** is employed as mediator of chirality can be rationalized by the assumption that **39** is formed as an intermediate in the catalytic cycle (Scheme 10). In complex **39** the steric interactions between the substituents of the stereodirecting amino alcohol and the β-phenyl group of the enolate are minimized. The involvement of a complex like **39** in the asymmetric transformation would also explain why only racemic product is formed with C_2-symmetric bis(amino alcohols) **9** and **10**. In this case presumably complexes like **39** could not form since direct coordination of the second amino alcohol to the nickel (instead of the enolate) should be preferred.



Scheme 10. Possible mechanism of the conjugate addition of diethylzinc to chalcone (**35**) in the presence of **11** as chiral ligand

Conclusion

In conclusion we have developed two alternative methods for the construction of chiral amino alcohols embodying the bicyclic bispidine framework. These tri- and tetradentate ligands can be employed advantageously for the steric steering of the enantioselectively catalyzed addition of diethylzinc to various aldehydes and chalcone. The degree of stereoselection is influenced by the bispidine template and the *N*-substituents linked to it.

Experimental Section

General Remarks: Melting points were determined in open capillaries using a Büchi 535 apparatus and are uncorrected. – ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AC 250, AM 400, or DRX 500 spectrometer at room temperature. – IR spectra were recorded with a Bruker IFS 88 spectrometer. – Mass spectra and high-resolution mass spectra (HRMS) were measured with a Finnigan MAT MS70 spectrometer. – Elemental analyses were performed with a Heraeus CHN-Rapid apparatus. – Specific optical predominantly rotation values were determined with a Perkin–Elmer polarimeter 241. – High-pressure liquid chromatography (HPLC) was performed with a Merck Hitachi instrument equipped with an L-3000 diode array detector and for all gas chromatography a Hewlett–Packard 5890 Series II gas chromatograph was used.

Materials: Solvents were dried by standard methods and used immediately or stored over molecular sieves. For column chromatography silica gel (40–60 μm, Baker or Fluka) was used. Commercial reagents were used without further purification except for *N*-methyl- and *N*-benzylpiperidin-4-one, which were distilled. L-(–)-Norephedrine was purchased from Fluka. L-(+)-Valine was donated by Degussa–Hüls AG. 1,1-Dimethyl-4-oxopiperidinium iodide (**15**)[12] and (*S*)-2-chloro-3-methylbutyl alcohol (**26**)[13] were prepared according to literature methods.

(1*S*,2*R*)-2-*tert*-Butyldimethylsiloxy-1-methyl-2-phenylethylamine (14):[11] To a solution of L-(–)-norephedrine (15 g, 99 mmol) in CH_2Cl_2 (150 mL) was added *tert*-butyldimethylsilyl chloride (15 g, 99 mmol) and NEt_3 (13.75 mL, 99 mmol). The mixture was stirred for 3 d at room temperature. Diethyl ether (20 mL) was added and the precipitate was removed by filtration. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel [3% MeOH in CH_2Cl_2, R_f = 0.22] to yield a waxy solid. Yield: 24.44 g, (92.1 mmol, 93%). – $[\alpha]_D^{20}$ = –52.0 (*c* = 1, $CHCl_3$), {ref.[11b] for (1*R*,2*S*) enantiomer: $[\alpha]_D^{20}$ = +49.0 (*c* = 1, $CHCl_3$)}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.27–7.21 (m, 5 H, arom. CH), 4.37 (d, ^3J = 5.2 Hz, 1 H, CHPh), 3.03–2.93 (m, 1 H, C*H*CH_3), 1.34 (br. s, 2 H, NH_2), 0.98 (d, ^3J = 6.7 Hz, 3 H, CHC*H*$_3$), 0.86 [s, 9 H, C(C*H*$_3$)$_3$], –0.03 (s, 3 H, $SiCH_3$), –0.22 (s, 3 H, $SiCH_3$).

***N*-[(1′*S*,2′*R*)-2′-*tert*-Butyldimethylsiloxy-1′-methyl-2′-phenylethyl]-piperidin-4-one (16):** To a refluxing mixture of norephedrine derivative **14**[11] (6 g, 22.6 mmol), K_2CO_3 (15.3 g, 110.7 mmol), ethanol (300 mL) and water (150 mL) was added over 30 min a solution of 1,1-dimethyl-4-oxopiperidinium iodide[12] (**15**) (14 g, 55.3 mmol) in water (150 mL). After addition was complete, the yellow solution was refluxed for an additional 30 min. Then the majority of ethanol was evaporated in vacuo and the aqueous residue was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel [hexane/ethyl acetate, 5:1 (v/v), R_f = 0.41] to yield a yellow oil. Yield: 5.31 g (15.3 mmol, 68%). – $[\alpha]_D^{20}$ = –10.6 (*c* = 1, $CHCl_3$). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.22 (m, 5 H, arom. CH), 4.67 (d, ^3J = 5.6 Hz,

1 H, CHPh), 2.94−2.90 (m, 2 H, NCH_{2eq}), 2.83−2.82 (m, 1 H, C*H*CH_3), 2.72−2.68 (m, 2 H, NCH_{2ax}), 2.31−2.28 (m, 4 H, $CH_2C{=}O$), 1.08 (d, ^3J = 6.6 Hz, 3 H, CHC*H*$_3$), 0.89 [s, 9 H, C(CH_3)$_3$], 0.04 (s, 3 H, SiCH_3), −0.27 (s, 3 H, SiCH_3). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 209.86 (C=O), 144.44 (arom. C), 127.67, 126.90, 126.59 (arom. CH), 77.43 (CHPh), 66.23 (*C*HCH$_3$), 49.42 (CH_2N), 42.23 (*C*H$_2$C=O), 25.84 [C(*C*H$_3$)$_3$], 18.09 [*C*(CH$_3$)$_3$], 9.68 (CH*C*H$_3$), −4.39, −4.93 (SiCH$_3$). − IR (KBr): ṽ = 2957, 2929, 2857, 2804, 1721 (C=O), 1472, 1387, 1361, 1255, 1074, 864, 837, 776, 701 cm^{-1}. − MS (70 eV); *m*/*z* (%): 347 (0.1) [M$^+$], 332 (0.6) [M$^+$ − CH$_3$], 290 (0.8) [M$^+$ − *t*Bu], 216 (1.0) [M$^+$ − $C_6H_{15}OSi$], 205 (1.9), 173 (2.1), 126 (100) [M$^+$ − $C_{13}H_{21}OSi$]; HRMS (70 eV): calcd. for $C_{20}H_{33}NO_2Si$: 347.2281; found: 347.2291.

3,7-Bis[(1′*S*,2′*R*)-2′-*tert*-butyldimethylsiloxy-1′-methyl-2′-phenylethyl]-3,7-diazabicyclo[3.3.1]nonan-9-one (17): To a mixture of coarse-grained paraformaldehyde (472 mg, 15.7 mmol) and dry methanol (12 mL) at 65°C was slowly added a solution of norephedrine derivative **14**[11] (1.96 g, 7.39 mmol), piperidinone **16** (2.48 g, 7.15 mmol) and acetic acid (0.83 mL, 15.5 mmol) in dry methanol (25 mL) over a period of 2 h. After completion of the addition, more paraformaldehyde (472 mg, 15.7 mmol) was added and the mixture was stirred for an additional 2 h. Water (100 mL) and 1 M KOH (20 mL) was added until the solution showed a basic pH. The mixture was extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The resulting orange oil was purified by flash chromatography on silica gel [hexane/ethyl acetate, 7:1 (v/v), R_f = 0.05] to yield a colourless oil. Yield: 1.77 g (2.78 mmol, 39%). − R_f = 0.32 (hexane/ethyl acetate/NEt_3, 7:1:0.2 (v/v/v). − $[\alpha]_D^{20}$ = −12.7 (*c* = 1.42, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30−7.18 (m, 10 H, arom. CH), 4.49 (d, ^3J = 6.3 Hz, 2 H, CHPh), 2.94 (dd, ^2J = 10.7 Hz, ^3J = 6.5 Hz, 2 H, NCH_{2eq}), 2.79 (dd, ^2J = 10.4 Hz, ^3J = 1.7 Hz, 2 H, NCH_{2eq}), 2.69−2.64 (m, 6 H, NCH_{2ax} and C*H*CH$_3$), 2.43−2.39 (m, 2 H, CHC=O), 0.95 (d, ^3J = 6.7 Hz, 6 H, CHC*H*$_3$), 0.86 [s, 18 H, C(CH_3)$_3$], 0.01 (s, 6 H, SiCH_3), −0.32 (s, 6 H, SiCH_3). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 214.22 (C=O), 144.21 (arom. C), 127.77, 127.05, 126.87 (arom. CH), 77.46 (CHPh), 65.10 (*C*HCH$_3$), 54.42, 53.74 (NCH_2), 47.47 (*C*HC=O), 25.84 [C(*C*H$_3$)$_3$], 18.07 [*C*(CH$_3$)$_3$], 9.89 (CH*C*H$_3$), −4.46, −4.90 (SiCH$_3$). − IR (KBr): ṽ = 3027, 2955, 2929, 2856 (Bohlmann band),[20] 1738 (C=O), 1472, 1361, 1256, 1072, 859, 837, 776, 701 cm^{-1}. − MS (70 eV); *m*/*z* (%): 636 (0.05) [M$^+$], 635 (0.1) [M$^+$ − H], 621 (0.1) [M$^+$ − CH$_3$], 579 (1.2) [M$^+$ − *t*Bu], 415 (100) [M$^+$ − $C_{13}H_{21}OSi$], 221 (2.8) [$C_{13}H_{21}OSi^+$], 193 (5.3); HRMS: calcd. for $C_{37}H_{60}N_2O_3Si_2$: 636.4143, found: 636.4125.

3,7-Bis[(1′*S*,2′*R*)-2′-hydroxy-1′-methyl-2′-phenylethyl]-3,7-diazabicyclo[3.3.1]nonan-9-one (18): To a solution of bispidinone **17** (1.63 g, 2.57 mmol) in THF (8 mL) was added tetrabutylammonium fluoride (1 M in THF, 6.3 mL). The mixture was stirred at room temperature overnight. The solution was concentrated to a volume of 5 mL and filtered through a plug of silica gel. After evaporation of the solvent, the crude product was purified by flash chromatography eluting first with $CHCl_3$/MeOH, 4:1 (v/v) (R_f = 0.23) and then with $CHCl_3$/MeOH/NEt_3, 4:1:0.2 (v/v/v) (R_f = 0.42) to yield a white foam. Yield: 836 mg (2.05 mmol, 80%). − $[\alpha]_D^{20}$ = −22.4 (*c* = 1.65, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.20 (m, 10 H, arom. CH), 4.96 (d, ^3J = 4.1 Hz, 2 H, CHPh), 4.55 (br. s, 2 H, OH), 3.32 (d, ^2J = 11.1 Hz, 2 H, NCH_{2eq}), 3.20 (d, ^2J = 11.1 Hz, 2 H, NCH_{2eq}), 2.95 (dd, ^2J = 11.2, ^3J = 3.7 Hz, 2 H, NCH_{2ax}), 2.83 (dd, ^2J = 11.2 Hz, ^3J = 3.6 Hz, 2 H, NCH_{2ax}), 2.78−2.75 (m, 2 H, C*H*CH$_3$), 2.44 (m, 2 H, CHC=O), 0.91 (d, ^3J = 6.9 Hz, 6 H, CHC*H*$_3$). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 214.35 (C=O), 142.32 (arom. C), 128.08, 126.97, 126.15 (arom. CH), 73.08 (CHPh), 64.00 (*C*HCH$_3$), 57.25, 55.02 (NCH_2), 48.07 (*C*HC=O), 10.20 (CH*C*H$_3$). − IR (drift): ṽ = 3399 (OH), 2974, 2937, 2818 (Bohlmann band),[20] 1731 (C=O), 1584, 1451, 1390, 1369, 1199, 1091, 1067, 764, 753, 703 cm^{-1}. − MS (70 eV); *m*/*z* (%): 408 (0.05) [M$^+$], 407 (0.2) [M$^+$ − H], 345 (0.1), 301 (100) [M$^+$ − OBzl], 195 (22) [(M$^+$ − OBzl) − C_7H_6O], 72 (94); HRMS: calcd. for $C_{25}H_{32}N_2O_3$: 407.2335 [M$^+$ − H], found: 407.2347.

3,7-Bis[(1′*S*,2′*R*)-2′-hydroxy-1′-methyl-2′-phenylethyl]-3,7-diazabicyclo[3.3.1]nonane (9): To a mixture of bispidinone **18** (1.76 g, 4.31 mmol), hydrazine monohydrate (1.05 mL, 21.55 mmol) and diethylene glycol (20 mL) at 60°C was added powdered KOH (1.81 g, 33.32 mmol). The mixture was heated to 160°C for 4 h. The temperature was raised to 210°C for 45 min to remove excess hydrazine hydrate. After cooling, the residue was treated with water (30 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to a volume of 50 mL. The remaining solution was cooled to 0°C and thoroughly purged with HCl gas for 15 min. The precipitate was collected by filtration and was added to a mixture of 1 M KOH (30 mL) and diethyl ether (30 mL). After the solid was completely dissolved, the phases were separated and the aqueous phase was extracted with diethyl ether (2 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The resulting solid bispidine **9** was pure enough to be used in subsequent asymmetric reactions. Yield: 1.28 g (3.24 mmol, 75%). Alternatively, an analytically pure sample can be obtained by flash chromatography on silica gel [$CHCl_3$/MeOH/NEt_3/H_2O, 6:5:1:2 (v/v/v/v), R_f = 0.37]. M.p. 101°C. − $[\alpha]_D^{20}$ = −45.0 (*c* = 0.86, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, ^3J = 7.5 Hz, 4 H, arom. CH), 7.31 (t, ^3J = 7.6 Hz, 4 H, arom. CH), 7.20 (t, ^3J = 7.2 Hz, 2 H, arom. CH), 6.25 (br. s, 2 H, OH), 5.14 (d, ^3J = 3.6 Hz, 2 H, CHPh), 3.38 (d, ^2J = 10.6 Hz, 2 H, NCH_{2eq}), 3.08 (d, ^2J = 10.5 Hz, 2 H, NCH_{2eq}), 2.66 (d, ^2J = 11.1 Hz, 2 H, NCH_{2ax}), 2.63−2.57 (m, 2 H, C*H*CH$_3$), 2.42 (d, ^2J = 11.3 Hz, 2 H, NCH_{2ax}), 1.94 (m, 2 H, C*H*CH$_2$), 1.60 (m, 2 H, CH_2 bridge), 0.87 (d, ^3J = 6.9 Hz, 6 H, CHC*H*$_3$). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.80 (arom. C), 127.79, 126.40, 126.22 (arom. CH), 72.03 (CHPh), 65.80 (*C*HCH$_3$), 57.36, 54.11 (NCH_2), 32.79 (CH_2 bridge), 30.97 (*C*HCH$_2$), 10.33 (CH*C*H$_3$). − IR (drift): ṽ = 3367 (OH), 3082, 2925, 2799 (Bohlmann band),[20] 1494, 1449, 1389, 1163, 1064, 1005, 745, 706 cm^{-1}. − MS (70 eV); *m*/*z* (%): 394 (0.1) [M$^+$], 393 (0.5) [M$^+$ − H], 317 (0.2), 287 (100) [M$^+$ − C_7H_7O], 181 (38) [(M$^+$ − C_7H_7O) − C_7H_6O], 72 (84); HRMS: calcd. for $C_{25}H_{34}N_2O_2$: 393.2542 [M$^+$ − H], found: 393.2528. − $C_{25}H_{34}N_2O_2$ (394.56): calcd. C 76.10, H 8.69, N 7.10; found C 76.34, H 8.61, N 7.08.

3-[(1′*S*,2′*R*)-2′-*tert*-Butyldimethylsiloxy-1′-methyl-2′-phenylethyl]-7-methyl-3,7-diazabicyclo[3.3.1]nonan-9-one (20): This compound was prepared by analogy to bispidinone **17** using MeOH (30 mL), paraformaldehyde (622 mg, 20.7 mmol), *N*-methylpiperidin-4-one **19** (1.07 g, 9.42 mmol), norephedrine derivative **14**[11] (2.5 g, 9.42 mmol), acetic acid (1.08 mL, 18.8 mmol), MeOH (20 mL) and after 2 h additional paraformaldehyde (622 mg, 20.7 mmol). The resulting yellow oil was purified by flash chromatography on silica gel eluting first with $CHCl_3$/MeOH, 4:1 (v/v) (R_f = 0.25) and then with $CHCl_3$/MeOH/NEt_3, 4:1:0.2 (v/v/v) (R_f = 0.31) to yield a colourless oil. Yield: 2.42 g (6.01 mmol, 64%). − $[\alpha]_D^{20}$ = −20.9 (*c* = 0.5, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33−7.26 (m, 5 H, arom. CH), 4.45 (d, ^3J = 7.5 Hz, 1 H, CHPh), 2.91−2.75 (m, 6 H, NCH_2 and C*H*CH$_3$), 2.62 (dd, ^2J = 10.7 Hz, ^3J = 3.3 Hz, 2 H, NCH_2), 2.46−2.42 (m, 3 H, CHC=O and NCH_2), 2.39 (dd, ^2J = 10.2 Hz, ^3J = 3.2 Hz, 1 H, NCH_2), 1.99 (s, 3 H, NCH_3) 1.11 (d, ^3J = 6.7 Hz, 3 H, CHC*H*$_3$), 0.81 [s, 9 H, C(CH_3)$_3$], 0.00 (s, 3 H, SiCH_3), −0.35 (s, 3 H, SiCH_3). − ^{13}C NMR (100.6 MHz,

$CDCl_3$): δ = 214.86 (C=O), 144.14 (arom. C), 127.99, 127.47, 127.36 (arom. CH), 77.51 (CHPh), 64.67 (*C*HCH_3), 59.27, 58.99, 56.97, 53.51 (NCH_2), 47.17, 46.57 (*C*HC=O), 44.56 (NCH_3), 25.77 [C(*C*$H_3)_3$], 18.01 [*C*$(CH_3)_3$], 10.80 (CH*C*H_3), −4.37, −4.90 ($SiCH_3$). − IR (KBr): $\tilde{\nu}$ = 2935, 2856 and 2809 (Bohlmann bands),[20] 1739 (C=O), 1472, 1367, 1257, 1072, 858, 837, 776, 701 cm^{-1}. − MS (70 eV); *m*/*z* (%): 401 (0.03) [M^+ − H], 387 (0.55) [M^+ − CH_3], 345 (0.4), 236 (0.5), 221 (0.74) [$C_{13}H_{21}OSi^+$], 181 (100) [M^+ − $C_{13}H_{21}OSi$], 72 (19); HRMS: calcd. for $C_{23}H_{38}N_2O_2Si$: 401.2624 [M^+ − H], found: 401.2640.

3-[(1′*S*,2′*R*)-2′-Hydroxy-1′-methyl-2′-phenylethyl]-7-methyl-3,7-diazabicyclo[3.3.1]nonan-9-one (21): This compound was prepared by analogy to **18** using bispidinone **20** (772 mg, 1.92 mmol) and TBAF solution (1 M in THF, 2.11 mL) and THF (2 mL). After filtration, the solvent was evaporated in vacuo and the resulting oil was dissolved in diethyl ether (50 mL). The remaining solution was cooled to 0°C and thoroughly purged with HCl gas for 15 min. The precipitate was collected by filtration and was added to a mixture of 1 M KOH solution (20 mL) and diethyl ether (20 mL). After the solid was completely dissolved, the phases were separated and the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The resulting colourless oil was pure enough for analysis and was used without further purification. Yield: 475 mg (1.65 mmol, 86%). − R_f = 0.20 [$CHCl_3$/MeOH, 4:1 (v/v)]. − $[\alpha]_D^{20}$ = −20.3 (*c* = 0.74, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.21 (m, 5 H, arom. CH), 5.78 (br. s, 1 H, OH), 4.85 (d, ^3J = 4.9 Hz, 1 H, CHPh), 3.40−3.36 (m, 1 H, NCH_2), 3.24 (d, ^2J = 10.9 Hz, 2 H, NCH_2), 3.15−3.11 (m, 1 H, NCH_2), 3.06 (d, ^2J = 12.6 Hz, 1 H, NCH_2), 3.03−2.98 (m, 1 H, C*H*CH_3), 2.81 (d, ^2J = 11.1 Hz, 1 H, NCH_2), 2.74−2.67 (m, 2 H, NCH_2), 2.42−2.40 (m, 1 H, CHC=O), 2.33−2.31 (m, 4 H, NCH_3 and CHC=O), 0.88 (d, ^3J = 7.0 Hz, 3 H, CHC*H*$_3$). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 214.67 (C=O), 141.90 (arom. C), 127.96, 126.78, 126.20 (arom. CH), 73.24 (CHPh), 61.67 (*C*HCH_3 and NCH_2), 61.36, 58.08, 53.40 (NCH_2), 48.67, 48.30 (*C*HC=O), 45.05 (NCH_3), 11.13 (CH*C*H_3). − IR (drift): $\tilde{\nu}$ = 3371 (OH), 2941, 2793 (Bohlmann band),[20] 1733 (C=O), 1454, 1370, 1256, 1154, 753, 702 cm^{-1}. − MS (70 eV); *m*/*z* (%): 288 (0.07) [M^+], 287 (0.24) [M^+ − H], 181 (100) [M^+ − C_7H_7O], 72 (58); HRMS: calcd. for $C_{17}H_{24}N_2O_2$: 288.1838, found: 288.1850.

3-[(1′*S*,2′*R*)-2′-Hydroxy-1′-methyl-2′-phenylethyl]-7-methyl-3,7-diazabicyclo[3.3.1]nonane (11): This compound was prepared by analogy to **9** using bispidinone **21** (475 mg, 1.65 mmol), hydrazine monohydrate (400 μL, 8.24 mmol) and diethylene glycol (5 mL). After workup, the crude product was purified by similar treatment with HCl gas, which led to the formation of an oil. This oil was separated from the liquid phase, washed with diethyl ether and a mixture of a 1 M KOH solution (10 mL) and diethyl ether (10 mL) was added. The procedure described above afforded a colourless oil, which was pure enough for analysis and was used as obtained for subsequent asymmetric reactions. Yield: 344 mg (1.25 mmol, 76%). − $[\alpha]_D^{20}$ = −41.8 (*c* = 1, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33−7.27 (m, 4 H, arom. CH), 7.21−7.17 (m, 1 H, arom. CH), 7.01 (br. s, 1 H, OH), 4.79 (d, ^3J = 4.8 Hz, 1 H, CHPh), 3.10−3.02 (m, 3 H, NCH_2), 2.87−2.78 (m, 3 H, C*H*CH_3 and NCH_2), 2.54−2.51 (m, 1 H, NCH_2), 2.28−2.12 (m, 2 H, NCH_2), 2.26 (s, 3 H, NCH_3), 1.84−1.82 (m, 1 H, C*H*CH_2), 1.75−1.73 (m, 1 H, C*H*CH_2), 1.53−1.51 (m, 2 H, CH_2 bridge), 0.77 (d, ^3J = 7.1 Hz, 3 H, CHC*H*$_3$). − ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.60 (arom. C), 127.63, 126.17 (arom. CH), 72.93 (CHPh), 62.26 (*C*HCH_3), 60.80, 60.61, 57.01, 51.69 (NCH_2), 46.80 (NCH_3), 32.79 (CH_2 bridge), 30.93, 30.58 (*C*HCH_2), 10.64 (CH*C*H_3). − IR (drift): $\tilde{\nu}$ = 3183 (OH), 2016, 2776 (Bohlmann band),[20] 1450, 1265, 1169, 1148, 1002, 743, 701 cm^{-1}. − MS (70 eV); *m*/*z* (%): 274 (0.02) [M^+], 273 (0.1) [M^+ − H], 167 (100) [M^+ − OBzl], 72 (64); HRMS: calcd. for $C_{17}H_{26}N_2O$: 274.2045, found: 274.2019.

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (23):[7] A suspension of benzylamine (10.9 mL, 0.1 mol), acetic acid (5.7 mL, 0.1 mol), concentrated HCl (4.2 mL, 0.05 mol) and paraformaldehyde (6.3 g, 0.21 mol) in MeOH (100 mL) was stirred for 5 min at 65°C. To this was added dropwise a solution of *N*-benzylpiperidin-4-one (**22**) (17.9 mL, 0.1 mol) and acetic acid (5.7 mL, 0.1 mol) in MeOH (100 mL) over 1 h. After stirring for 10 h, another portion of paraformaldehyde (6.3 g, 0.21 mol) was added and stirring was continued for 6 h. The mixture was concentrated in vacuo and the residue was dissolved in water (50 mL). The aqueous phase was washed with diethyl ether (2 × 50 mL) and made strongly basic with 20% KOH solution under ice bath cooling. After extraction with CH_2Cl_2 (4 × 100 mL), drying the combined organic layers over Na_2SO_4 and evaporation of the solvent, the residue was filtered through silica gel [ethyl acetate/hexane, 1:1 (v/v)]. Crystallization of the resulting yellow oil from hexane/ethyl acetate, 99:1 (v/v) afforded a white solid. Yield: 16.33 g (0.051 mol, 51%); m.p. 79°C (ref.[7c]: m.p. 80−81°C). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36−7.22 (m, 10 H, arom. CH), 3.55 (s, 4 H, NCH_2Ph), 3.07−3.01 (m, 4 H, cycl. NCH_{2eq}), 2.84−2.77 (m, 4 H, cycl. NCH_{2ax}), 2.61−2.52 (m, 2 H, CHCO).

3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane (24):[7a] To a solution of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**23**) (16.3 g, 50.9 mmol) and hydrazine monohydrate (12.3 mL, 255 mmol) in diethylene glycol (160 mL) at 80°C was added KOH (17 g, 305 mmol). The solution was heated to 150°C and stirred for 3 h. After removing the hydrazine and water by distillation at 200°C, cooling the reaction mixture to room temperature and addition of water (100 mL), the aqueous phase was extracted with diethyl ether (5 × 100 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated in vacuo. The resulting yellow oil was used without further purification. Yield: 14.6 g (47.85 mmol, 94%). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.47−7.20 (m, 10 H, arom. CH), 3.46 (s, 4 H, NCH_2Ph), 2.81 (dd, ^2J = 11 Hz, ^3J = 2 Hz, 4 H, cycl. NCH_{2eq}), 2.33 (dd, ^2J = 11 Hz, ^3J = 4 Hz, 4 H, cycl. NCH_{2ax}), 1.92−1.81 (m, 2 H, C*H*CH_2), 1.58−1.52 (m, 2 H, CH_2 bridge).

3,7-Diazabicyclo[3.3.1]nonane (2):[7a] Pd/C (10%, 2.5 g) was added to a solution of acetic acid (28 mL, 475 mmol) and 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonane (**24**) (14.6 g, 47.6 mmol) in MeOH (30 mL). The suspension was stirred for 18 h under an atmosphere of hydrogen. After filtration through Celite and concentration in vacuo, the residue was dissolved in water (50 mL) and the pH was adjusted to 10 by addition of 20% KOH solution. The aqueous phase was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. Kugelrohr distillation ($p = 5 \times 10^{-2}$ mbar) yielded a colorless oil. Yield: 5.16 g, 40.9 mmol, 86%. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.20−3.05 (m, 8 H, cycl. NCH_2), 2.57 (br. s, 2 H, NH), 1.87−1.82 (m, 2 H, CH), 1.59−1.53 (m, 2 H, CH_2 bridge).

3-Benzyl-7-methyl-3,7-diazabicyclo[3.3.1]nonane (25):[7a,7b] To a suspension of paraformaldehyde (18 g, 0.6 mol) and concentrated HCl (8 mL, 0.1 mol) in MeOH (200 mL) at 65°C was added over a period of 2 h a solution of benzylamine (21.9 mL, 0.2 mol), *N*-methylpiperidin-4-one (**19**) (24.6 mL, 0.2 mol) and acetic acid (22.9 mL, 0.4 mol) in MeOH (200 mL). After stirring for 6 h, another portion of paraformaldehyde (3 g, 0.1 mol) was added. The

mixture was stirred for an additional 4 h. After evaporation of the solvent, water (200 mL) was added and the pH was adjusted to 10 with 20% KOH solution. The aqueous phase was extracted with CH_2Cl_2 (4 × 100 mL) and the combined organic layers were dried with Na_2SO_4. Concentration in vacuo yielded a viscous yellow oil, which was used without further purification in the next step. KOH (63 g, 1.12 mol) was added to a solution of the Mannich-product and hydrazine monohydrate (45 mL, 0.93 mol) in diethylene glycol (400 mL). The mixture was stirred for 3 h at 140°C. After removing the hydrazine and water by distillation at 200°C, cooling the reaction mixture to room temperature and addition of water (100 mL), the aqueous phase was extracted with diethyl ether (5 × 100 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was evaporated in vacuo. Distillation under reduced pressure yielded a colourless oil. Yield: 25.52 g (111 mmol, 55%); b.p. 105°C ($p = 5 \times 10^{-2}$ mbar) [ref.[7d]: b.p. 107−108°C ($p = 5 \times 10^{-1}$ mm)]. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.49−7.29 (m, 5 H, arom. CH), 3.52 (s, 2 H, CH_2Ph), 2.85−2.68 (m, 4 H, cycl. NCH_{2eq}), 2.53−2.19 (m, 4 H, cycl. NCH_{2ax}), 2.24 (s, 3 H, CH_3), 1.97−1.88 (m, 2 H, NCH_2CH), 1.55 (dd, ^2J = 12 Hz, 1 H, CH_2 bridge), 1.42 (dd, ^2J = 12 Hz, 1 H, CH_2 bridge).

3-Methyl-3,7-diazabicyclo[3.3.1]nonane (8):[7b] Pd/C (10%, 5 g) was added to a solution of 3-benzyl-7-methyl-3,7-diazabicyclo-[3.3.1]nonane (**25**) (25.5 g, 111 mmol) in 85% acetic acid (50 mL). The resulting suspension was stirred at room temperature for 6 h under an atmosphere of hydrogen. After filtration through Celite and concentration in vacuo, water (50 mL) was added. The aqueous phase was made strongly basic with 20% KOH solution under ice bath cooling and extracted with diethyl ether (4 × 100 mL). After drying the combined organic layers over Na_2SO_4 and evaporation of the solvent under reduced pressure the residue was purified by vacuum distillation. Yield: 13.2 g, 94.3 mmol, 85%; b.p. 95−97°C (p = 36 mbar) [ref.[7b]: b.p. 97−99°C (p = 28 mm)]. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.08−2.89 (m, 8 H, NCH_2), 2.30−2.22 (m, 2 H, CH_2 bridge), 2.09 (s, 3 H, CH_3), 1.65−1.57 (m, 3 H, CH and NH).

3,7-Bis[(2′*R*)-2′-hydroxy-3′-methylbutyl]-3,7-diazabicyclo[3.3.1]-nonane (10): To a solution of (*S*)-2-chloro-3-methylbutyl alcohol[13] (**26**) (2.94 g, 24 mmol) in MeOH (24 mL) at 0°C was added NaOMe (30% in MeOH, 5.3 mL, 28.8 mmol). After warming up to room temperature over 1 h, a solution of 3,7-diazabicyclo[3.3.1]nonane (**2**) (1.01 g, 8 mmol) in MeOH (4 mL) was added. The resulting mixture was stirred overnight. The solution was quenched with 2 M HCl (20 mL), stirred at room temperature for 30 min and washed with diethyl ether (2 × 30 mL). The aqueous phase was made basic with 20% KOH solution and was extracted with diethyl ether (3 × 30 mL). After drying the combined organic layers over Na_2SO_4 and evaporation of the solvent in vacuo, the residue was purified by chromatography on silica gel [$CHCl_3$/MeOH/NEt_3, 10:1:1 (v/v/v), R_f = 0.16]. Yield: 1.76 g (5.9 mmol, 74%); m.p. 53°C. − $[\alpha]_D^{20}$ = −67.4 (c = 1, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.46 (br. s, 2 H, OH), 3.44 (ddd, ^2J = 9.7 Hz, ^3J = 6.3 Hz, ^3J = 3.2 Hz, 2 H, C*H*OH), 3.11 (d, ^2J = 11.0 Hz, 2 H, cycl. NCH_{2eq}), 2.91 (d, ^2J = 10.9 Hz, 2 H, cycl. NCH_{2eq}), 2.64 (d, ^2J = 11.1 Hz, 2 H, cycl. NCH_{2ax}), 2.34−2.25 (m, 6 H, cycl. NCH_{2ax} and NCH_2), 1.89−1.83 (m, 2 H, NCH_2CH), 1.62−1.56 [m, 4 H, $CH(CH_3)_2$ and CH_2 bridge], 0.96 (d, ^3J = 6.7 Hz, 6 H, CH_3), 0.87 (d, ^3J = 6.8 Hz, 6 H, CH_3). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 71.3 (COH), 62.5, 60.2 (cycl. NCH_2), 56.2 (NCH_2), 32.7 [$CH(CH_3)_2$], 32.7 (CH_2 bridge), 30.5 (NCH_2CH), 18.6, 18.3 (CH_3). − IR (KBr): $\tilde{\nu}$ = 3509 (OH), 3130, 2918, 2785 (Bohlmann band),[20] 1463, 1296, 1168, 1003, 738 cm^{-1}. − MS (70 eV); *m*/*z* (%): 298 (2) [M^+], 255 (60) [M^+ − *i*Pr], 225 (51) [$C_{13}H_{25}N_2O^+$], 208 (12), 207 (16), 154 (100) [$C_9H_{16}NO^+$], 153 (25) [$C_9H_{15}NO^+$], 151 (12), 130 (42), 124 (8) [$C_7H_{12}N_2^+$], 97 (10), 58 (60) [$C_3H_8N^+$]; HRMS (70 eV) calcd. for $C_{17}H_{34}N_2O_2$: 298.2620, found: 298.2640.

(2′*R*)-3-(2′-Hydroxy-3′-methylbutyl)-7-methyl-3,7-diazabicyclo-[3.3.1]nonane (12): To a solution of (*S*)-2-chloro-3-methylbutyl alcohol[13] (**26**) (1.84 g, 15 mmol) in MeOH (15 mL) at 0°C was added NaOMe (30% in MeOH, 3.3 mL, 18 mmol). After warming up to room temperature over 1 h, a solution of 3-methyl-3,7-diazabicyclo[3.3.1]nonane (**8**) (1.4 g, 10 mmol) in MeOH (5 mL) was added. The resulting mixture was stirred overnight. The solution was quenched with 2 M HCl (20 mL), stirred 30 min at room temperature and washed with diethyl ether (2 × 20 mL). The aqueous phase was made basic with 20% KOH and was extracted with diethyl ether (3 × 30 mL). After drying the combined organic layers with Na_2SO_4 and evaporation of the solvent in vacuo, the residue was purified by chromatography on silica gel [$CHCl_3$/MeOH/NEt_3/H_2O, 7:5:2:1 (v/v/v/v), R_f = 0.26]. Yield: 1.66 g (7.3 mmol, 73%). − $[\alpha]_D^{20}$ = −44.5 (c = 1, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.94 (br. s, 1 H, COH), 3.25 (ddd, ^2J = 10.8 Hz, ^3J = 7.2 Hz, ^3J = 3.6 Hz, 1 H, C*H*OH), 2.91−2.86 (m, 3 H, cycl. NCH_2), 2.78−2.73 (m, 2 H, cycl. NCH_2), 2.40−2.33 (m, 2 H, cycl. NCH_2), 2.10 (s, 3 H, NCH_3), 2.16−2.04 (m, 3 H, cycl. NCH_2 and NCH_2), 1.75−1.73 (m, 2 H, NCH_2CH), 1.53−1.47 [m, 3 H, $CH(CH_3)_2$ and CH_2 bridge], 0.96 (d, ^3J = 6.7 Hz, 3 H, CH_3), 0.80 (d, ^3J = 6.8 Hz, 3 H, CH_3). − ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 71.2 (COH), 60.7, 60.65, 60.2, 59.7 (cycl. NCH_2), 54.4 (NCH_2), 46.7 (NCH_3), 33.0 [$CH(CH_3)_2$], 32.2 (CH_2 bridge), 30.9, 30.1 (NCH_2CH), 19.5, 18.2 [$CH(CH_3)_2$]. − IR (KBr): $\tilde{\nu}$ = 3249 (OH), 2919, 2776 (Bohlmann band),[20] 1462, 1293, 1268, 1149, 1071, 1005, 753, 737 cm^{-1}. − MS (70 eV); *m*/*z* (%): 226 (3) [M^+], 183 (30) [M^+ − *i*Pr], 154 (58) [$C_9H_{16}NO^+$], 153 (38) [$C_9H_{15}NO^+$], 124 (22) [$C_7H_{12}N_2^+$], 110 (10), 97 (27), 96 (12), 94 (14), 58 (100) [$C_3H_8N^+$]; HRMS (70 eV) calcd. for $C_{13}H_{26}N_2O$: 226.2045, found: 226.2057.

General Procedure for the Addition of Diethylzinc to Aldehydes in the Presence of Chiral Ligands: To a solution of the ligand (0.127 mmol, 5 mol-%) in degassed toluene (10 mL) was added diethylzinc (1 M in hexane, 3.04 mL). The mixture was stirred for 15 min at room temperature. It was then cooled to −78°C and the appropriate aldehyde (2.53 mmol) was added. The mixture was allowed to warm to 0°C and was stirred at that temperature for 24 h. Saturated NH_4Cl solution (20 mL) was added and the resulting mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated carefully in vacuo. The residue was chromatographed on silica gel to yield the corresponding alcohol as a colourless oil. Determination of enantiomeric ratios was performed by gas chromatography (capillary column: CS FS Cyclodex β-I/p) either with the purified alcohol or after modification to either the acetic acid or trifluoroacetic acid ester derivative. The following data refers to alcohols prepared with ligand **11** (see Table 1 for the results obtained with the different ligands).

1-Phenyl-1-propanol (29a): Yield: 96%; 98% *ee*, (*R*)-(+) enantiomer predominating [hexane/ethyl acetate, 4:1 (v/v), R_f = 0.42]. − $[\alpha]_D^{20}$ = +47.0 (c = 5, $CHCl_3$, 98% *ee*) {ref.[15]: $[\alpha]_D^{20}$ = −47.6 [c = 6.11, $CHCl_3$, 98% *ee* for (*S*)-(−) enantiomer]}. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.36−7.26 (m, 5 H, arom. CH), 4.60 (t, ^3J = 6.6 Hz, 1 H, C*H*OH), 1.89−1.69 (m, 2 H, CH_2), 1.83 (br. s, 1 H, OH), 0.92 (t, ^3J = 7.5 Hz, 3 H, CH_3). − GC (100°C, isotherm): t_R = 41.5 min [(*R*) enantiomer], t_R = 44.8 min [(*S*) enantiomer].

3-Nonanol (29b): Yield: 95%; 85% *ee*, (*R*)-(−) enantiomer predominating [hexane/ethyl acetate, 10:1 (v/v), R_f = 0.34]. − $[\alpha]_D^{20}$ = −7.9

(c = 1.5, MeOH, 85% *ee*) {ref.[21]: $[\alpha]_D^{20}$ = −8.4 (c = 1.5, MeOH)}. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.56−3.50 (m, 1 H, C*H*OH), 1.49−1.28 (m, 13 H, CH_2 and OH), 0.94 (t, ^3J = 8.5 Hz, 3 H, CH_3), 0.89 (t, ^3J = 7.5 Hz, 3 H, CH_3). − GC (110°C, isotherm, derivative: 3-nonyl acetate): t_R = 11.4 min [(*S*) enantiomer], t_R = 12.0 min [(*R*) enantiomer].

5-Methylhexan-3-ol (29c): Yield: 94%; 83% *ee*, (*R*)-(−) enantiomer predominating [pentane/diethyl ether, 5:1 (v/v), R_f = 0.28]. − $[\alpha]_D^{20}$ = −18.2 (c = 2.52, EtOH, 83% *ee*) {ref.[22]: $[\alpha]_D^{20}$ = −20.3 (c = 5.25, EtOH)}. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.64−3.58 (m, 1 H, C*H*OH), 1.81−1.72 [m, 1 H, C*H*$(CH_3)_2$], 1.53−1.18 (m, 5 H, CH_2 and OH), 0.98−0.90 (m, 9 H, CH_3). − GC (35°C, isotherm, derivative: 5-methylhex-3-yl trifluoroacetate): t_R = 18.5 min [(*R*) enantiomer], t_R = 12.0 min [(*S*) enantiomer].

General Procedure for the Addition of Diethylzinc to Chalcone (35) with Catalytic Amounts of Ni(acac)$_2$ and Chiral Amino Alcohols: A solution of Ni(acac)$_2$ (18 mg, 0.07 mmol) and the chiral ligand (0.16 mmol of ligands **11** and **12**, 0.13 mmol of ligands **9** and **10**) in MeCN (2 mL) was stirred at reflux for 1 h. After cooling to room temperature chalcone (**35**) (208 mg, 1 mmol) was added and the solution was stirred for 15 min. After cooling to −35°C $ZnEt_2$ (1 M in hexane, 1.5 mL, 1.5 mmol) was added and the resulting mixture was stirred at −30°C for 16 h. The solution was poured into 2 M HCl (20 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. Purification by chromatography on silica gel [hexane/ethyl acetate, 30:1 (v/v), R_f = 0.24] yielded 1,3-diphenylpentan-1-one (**36**) as a colorless oil (results are shown in Table 2). The following data refer to the reaction performed with ligand **11**. The enantiomeric ratio was determined by HPLC, column: DAICEL CHIRACEL OD, 0.2% EtOH in hexane, flow rate 0.5 mL/min, UV detector (255 nm); retention times for **36**: t_R = 27.4 min [(*S*) enantiomer], t_R = 31.2 min [(*R*) enantiomer]. − $[\alpha]_D^{20}$ = +8.9 (c = 2.5, EtOH, 84% *ee*) {ref.[19]: $[\alpha]_D^{20}$ = +10.5 (c = 2.5, EtOH)}. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.93−7.87 (m, 2 H, arom. CH), 7.55−7.50 (m, 1 H, arom. CH), 7.45−7.39 (m, 2 H, arom. CH), 7.31−7.15 (m, 5 H, arom. CH), 3.28−3.20 (m, 3 H, CH_2CO and CH−Ph), 1.83−1.54 (m, 2 H, C$H_2$$CH_3$), 0.79 (t, ^3J = 7 Hz, CH_3).

General Procedure for the Addition of Diethylzinc to Chalcone (35) with Catalytic Amounts of Ni(acac)$_2$, Chiral Amino Alcohols and 2,2′-Bipyridyl: A solution of Ni(acac)$_2$ (2 mg, 0.008 mmol) and the chiral ligand (0.16 mmol of ligands **11** and **12**) in MeCN (2 mL) was stirred at reflux for 30 min. After addition of 2,2′-bipyridyl (1.3 mg, 0.008 mmol), the resulting solution was refluxed for an additional 30 min. The mixture was cooled to room temperature and chalcone (**35**) (167 mg, 0.8 mmol) was added. The isolation and purification of the product was achieved following the procedure described above. The results are shown in Table 2.

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[1] *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**.
[2] A. Togni, M. Venanzi, *Angew. Chem.* **1994**, *106*, 517−547; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497−527.
[3] [3a] D. Hoppe, F. Hintze, P. Tebben, M. Paetow, H. Ahrens, J. Schwertdfeger, P. Sommerfeld, J. Haller, W. Guarnieri, S. Kolczeewski, T. Hense, *Pure Appl. Chem.* **1994**, *66*, 1479−1486. − [3b] S. Thayumanavan, S. Lee, C. Liu, P. Beak, *J. Am. Chem. Soc.* **1994**, *116*, 9755−9756. − [3c] D. J. Gallagher, S. Wu, N. A. Nikolic, P. Beak, *J. Org. Chem.* **1995**, *60*, 8148−8154.
[4] A. Togni, *Tetrahedron: Asymmetry* **1991**, *2*, 683−690.
[5] S. E. Denmark, N. Nakajima, O. J.-C. Nicaise, *J. Am. Chem. Soc.* **1994**, *116*, 8797−8798.
[6] [6a] F. Bohlmann, N. Ottawa, R. Keller, *Justus Liebigs Ann. Chem.* **1954**, *586*, 162−176. − [6b] F. Galinovsky, H. Langer, *Monatsh. Chem.* **1955**, *86*, 449−453. − [6c] H. Stetter, H. Hennig, *Chem. Ber.* **1955**, *88*, 789−795. − [6d] H. Stetter, R. Merten, *Chem. Ber.* **1957**, *90*, 868−875.
[7] [7a] P. C. Ruenitz, E. E. Smissman, *J. Heterocycl. Chem.* **1976**, *13*, 1111−1113. − [7b] E. E. Smissman, P. C. Ruenitz, *J. Org. Chem.* **1976**, *41*, 1593−1597. − [7c] G. L. Garrison, K. D. Berlin, B. J. Scherlag, R. Lazzara, E. Patterson, S. Sangiah, C.-L. Chen, F. Schubot, J. Siripitayananon, M. B. Hossain, D. van der Helm, *J. Org. Chem.* **1993**, *58*, 7670−7678. − [7d] Patent, Knoll; FR 2274300, **1976**; DE 2428792; **1976**; *Chem. Abstr.* **1976**, *84*, 150675.
[8] K.-J. Haack, R. Goddard, K.-R. Pörschke, *J. Am. Chem. Soc.* **1997**, *119*, 7992−7999.
[9] [9a] R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34−55; *Angew. Chem. Int. Ed. Engl.* **1991**, *33*, 49−70. − [9b] C. Bolm, G. Schlingloff, K. Harms, *Chem. Ber.* **1992**, *125*, 1191−1203. − [9c] K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833−856.
[10] [10a] K. Soai, T. Hayasaka, S. Ugajin, *J. Chem. Soc., Chem. Commun.* **1989**, 516−517. − [10b] C. Bolm, M. Ewald, M. Felder, *Chem. Ber.* **1992**, *125*, 1205−1215. − [10c] A. H. M. de Vries, J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron* **1994**, *50*, 4479−4491. − [10d] A. H. M. de Vries, R. Imbos, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, *8*, 1467−1473.
[11] [11a] L. A. Silks, J. Peng, J. D. Odom, R. B. Dunlap, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2495−2498. − [11b] E. de Vries, P. Steenwinkel, J. Brussee, C. Kruse, A. van der Gen, *J. Org. Chem.* **1993**, *58*, 4315−4325.
[12] M. D. Thompson, E. M. Holt, K. D. Berlin, *J. Org. Chem.* **1985**, *50*, 2580−2581.
[13] [13a] C. Birk, J. Voss, *Tetrahedron* **1996**, *52*, 12745−12760. − [13b] B. Koppenhoefer, V. Schurig, *Org. Synth.* **1987**, *67*, 151−159. − [13c] B. Koppenhoefer, V. Schurig, *Org. Synth.* **1987**, *67*, 160−172.
[14] W. Oppolzer, P. Dudfield, *Tetrahedron Lett.* **1985**, *26*, 5037−5040.
[15] M. Kitamura, S. Suga, K. Kawai, R. Noyori, *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072.
[16] [16a] P. A. Chaloner, S. A. R. Perera, *Tetrahedron Lett.* **1987**, *28*, 3013−3014. − [16b] K. Soai, M. Nishi, Y. Ito, *Chem. Lett.* **1987**, 2405−2406. − [16c] P. A. Chaloner, E. Langadianou, S. A. R. Perera, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2731−2736.
[17] A. H. M. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, *8*, 1377−1378.
[18] J. F. G. A. Jansen, B. L. Feringa, *J. Org. Chem.* **1990**, *50*, 4168−4175.
[19] M. J. Brienne, C. Ouannes, J. Jacques, *Bull. Soc. Chim. Fr.* **1967**, 613−615.
[20] F. Bohlmann, *Chem. Ber.* **1958**, *91*, 2157−2167.
[21] B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 7473−7484.
[22] J. L. Coke, R. S. Shue, *J. Org. Chem.* **1973**, *38*, 2210−2211.

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