Solid-Phase Development of Chiral Phosphoramidite Ligands for Enantioselective Conjugate Addition Reactions

Oliver Huttenloch, Eltepu Laxman, and Herbert Waldmann*[a]

Abstract: The development of a method for the optimization of chiral ligands for the steric steering of enantioselective Cu-catalyzed conjugate additions of Zn-alkyls to enones is described. The method is based on combinatorial principles and solid-phase techniques. It includes the combinatorial synthesis of chiral bispidine-derived ligands embodying a phosphoramidite group on the solid phase and their investigation in immobilized form in the conjugate addition of $ZnEt_2$ to cyclohexenone as test reaction. The best identified ligands were also synthesized separately and investigated in its soluble form. The results obtained for the polymer-bound ligands correctly mirrored the performance of the soluble ligands. The library embodied members giving *ee* values varying between 3 and 67%. The "positional scanning" approach proved to be invalid for the study of the ligand system, indicating that this approach in general should be applied with care. Taken together, the method allowed for rapid and efficient optimization of the ligands and led to the development of the first enantioselective, Cu-catalyzed conjugate addition reaction with a polymer-bound ligand.

Keywords: asymmetric catalysis · combinatorial chemistry · conjugate addition · enantioselectivity · solid-phase synthesis

Introduction

The development of enantioselective catalyzed transformations is among the most important areas of organic synthesis, and within this field the use of chiral ligands for metal atoms to direct the steric course of chemical transformations has proven to be a key methodology. The introduction of new approaches to accelerate identification and optimization of such ligands has received particular attention. Very recently, the application of combinatorial principles to address this challenge has opened up entirely new opportunities to the field. In particular, the synthesis of ligand libraries on solid supports and their application as heterogeneous catalysts in screening systems has emerged as a powerful technique for the rapid development of finally soluble ligands for enantioselective catalysis.[1–9]

A key demand to be met by this strategy is that the results obtained with the immobilized ligands should correctly display the same trends in stereoselection as the corresponding soluble catalyst systems; ideally they should be (nearly) identical.[2–8] This demand was partly met in the development of peptide-derived salicylaldimine ligands for different transformations by Hoveyda et al.[2] and Jacobsen et al.[3] For solid phase bound salen ligands such a correlation could not be determined.[6] While the use of immobilized bis-oxazoline ligands in Mukaiyama aldol reactions gave results very similar to the homogeneously catalyzed cycloadditions,[5] in the study of polymer-bound sulfonamides in combination with diethylzinc, for this purpose the desired correlation was not given.[7]

The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is one of the most important transformations of organic synthesis. For the enantioselective steering of this reaction various methods have been developed,[10] and the Cu-catalyzed addition of dialkylzinc reagents to α,β-unsaturated enones and related compounds in the presence of chiral phosphoramidite ligands[10–12] pioneered by Alexakis et al.[11] and further developed in particular by Feringa et al.[12] but also by other groups[10] has emerged as a particularly efficient process. The application of combinatorial principles to the development of chiral ligands for Cu-catalyzed enantioselective conjugate addition processes has been pursued only in a single case.[13] Gennari et al. employed solid phase extraction techniques for the generation of soluble sulfonamide ligands. However, the approach described above, which has proven so successful for other types of transformations, that is the synthesis of a library of ligands on solid phase and its use in appropriate screening systems to ultimately develop soluble chiral ligands, has not been applied to enantioselectively catalyzed conjugate addition reactions.

Here we describe in full detail[14] the combinatorial synthesis of a library of polymer-bound bispidine-derived phos-

[a] Prof. Dr. H. Waldmann, Dr. O. Huttenloch, Dr. E. Laxman
Max-Planck-Institut für molekulare Physiologie
Abteilung Chemische Biologie
Otto-Hahn-Strasse 11, 44227 Dortmund (Germany)
and
Universität Dortmund, Fachbereich 3, Organische Chemie
Fax: (+49)-231-133-2499
E-mail: herbert.waldmann@mpi-dortmund.mpg.de

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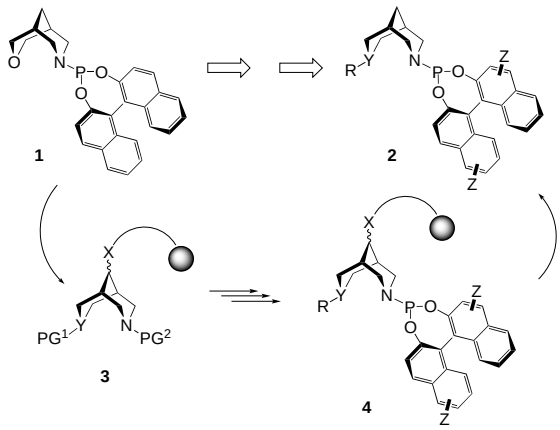
phoramidite ligands and its evaluation in the Cu-catalyzed enantioselective addition of dialkylzinc reagents to enones. We demonstrate that the results and trends gleaned from assaying the polymer-bound ligands provide a sound and reliable basis for the development of corresponding homogeneously soluble ligands.

Results and Discussion

We have recently shown that phosphoramidites, such as **1**, embodying a binaphthol unit and a bispidine-derived modulating substituent, can successfully be employed for the steric steering of Cu-catalyzed enantioselective conjugate addition reactions.[15] In order to find more efficient catalysts embodying the same underlying structural motifs it was decided to synthesize a library of ligands **2** (Scheme 1) on a polymeric support.



Scheme 1. Solid-phase optimisation strategy for bispidine phosphoramidites **1** and **2**.

The strategy envisioned to attach the ligands at the 9-position to the solid support. On the one hand, in the course of the bispidine synthesis the 9-keto intermediate is formed[16–18] which opens up various alternatives for attachment of a linker group. On the other hand the 9-position is on the face of the molecule opposite to the catalytically active metal atom after complexation. It should, therefore, not or only to a minor extent influence the course of stereoselective transformations. After unsuccessful attempts to link the bispidine system as an ester to the solid support,[19] coupling by a Wittig olefination turned out to be the method of choice (see below).

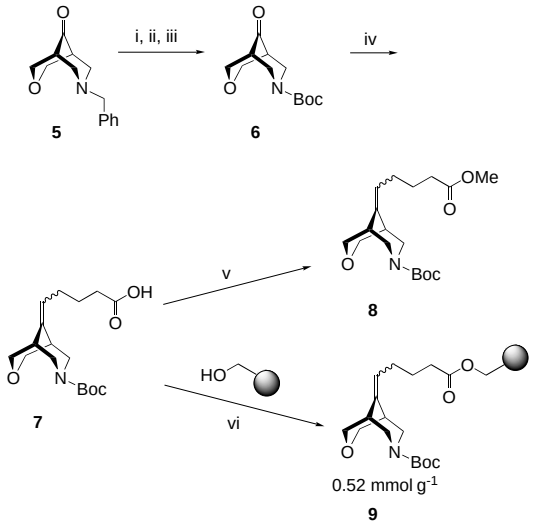
It was planned to vary the substitution pattern of the binaphthyl-phosphoramidite attached to one nitrogen of the underlying bicycled bispidine system and to vary the nature of the second heteroatom (O, N, S) as well as the substituent bound to it, if nitrogen was chosen (Scheme 1).

For the planning of the asymmetric reactions, the polymeric carrier should be regarded as part of the solvent system and it should have properties similar to the solvent employed.[20] Since toluene is the regular solvent used with dialkylzinc reagents an unpolar hydroxymethyl polystyrene matrix was chosen to which the bispidine was attached by esterification.

To determine, if the results to be expected from investigating such immobilized ligands would be comparable to the values recorded for soluble ligand **1** phosphoramidites **11** and **12** were synthesized as shown in Schemes 2 and 3. Compound **1** has been investigated thoroughly in the conjugate addition of diethylzinc to cyclohexenone and gave the addition product with an *ee* value of 43 %.[15, 21]

The hydrogenation-sensitive benzyl group present in oxabispidinone **5** is incompatible with the usual requirements of solid-phase synthesis and was replaced by an acid-labile Boc urethane.

N-Dealkylation was achieved by treatment with 1-chloroethylchloroformate and subsequent heating in methanol.[23] The resulting amine was acylated with di-*tert*-butylcarbonate to give intermediate **6** (Scheme 2). The subsequent Wittig



Scheme 2. Synthesis of the model systems **8** and **9**: i) $ClCOOCH(Cl)CH_3$, CH_2Cl_2, Δ, 2 h; ii) MeOH, Δ, 2 h; iii) Boc_2O, KOH, H_2O, dioxane, RT, 12 h, 87 %; iv) $BrPh_3P(CH_2)_4COOH$, KO*t*Bu, THF, 0 °C → RT, 2.5 h, 54 %; v) EEDQ, MeOH, RT, 12 h, 82 %; vi) DIC, DMAP, CH_2Cl_2, 12 h, RT, 71 %, then Ac_2O, pyridine.

reaction proceeded only with moderate yield which may be due to the low reactivity of the 9-keto group in bispidinones[14] observed by us in related cases as well.

Carboxylic acid **7** obtained thereby, was then either converted to methyl ester **8** employing EEDQ as activating reagent, or it was linked to hydroxymethyl polystyrene under Steglich conditions to give polymer **9** with a loading of 0.52 mmol g^{-1}. Unreacted hydroxy groups were capped by acylation with acetic anhydride. After removal of the Boc group from **8** and **9**, coupling with (*R*)-[binaphthyl-2,2′-diyl]chlorophosphite CIP(BINOL) (**10a**)[24] yielded phosphoramidites **11** and **12** (Scheme 3). Compound **11** was obtained as mixture of isomers which could not be separated and was employed as stereodirecting ligand in the conjugate addition of $ZnEt_2$ to cyclohexenone **13** as such. In this transformation chiral ketone **14** was obtained with 46 % *ee* at complete conversion (Scheme 4), that is with slightly higher stereoselectivity than with parent oxabispidine **1**. Thus

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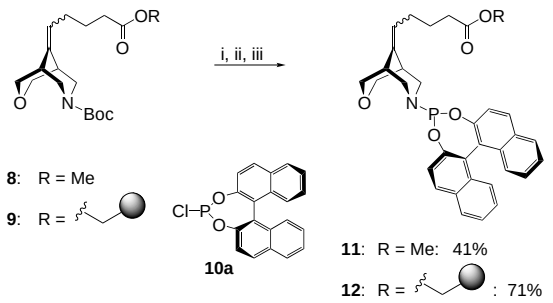
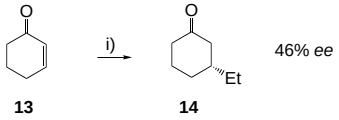


Scheme 3. Synthesis of phosphoramidites **11** and **12**: i) TFA, CH_2Cl_2, 0.5 h, RT, quant.; ii) Et_3N CH_2Cl_2 (only for **9**); iii) **10a**, Et_3N, toluene, 12 h, RT.

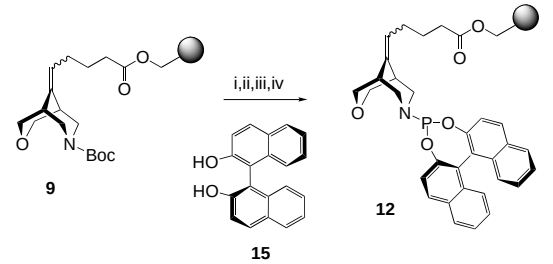


Scheme 4. Conjugate addition of diethylzinc to cyclohexen-2-one with ligand **11**: i) Et_2Zn, $Cu(OTf)_2$ (3 mol %), **11** (3.3 mol %), toluene, CH_2Cl_2, $-30\,^{\circ}C$, 2 h, complete conversion.

,introduction of an alkenyl group into the 9-position of the bicyclic system does not influence the stereoselectivity and the catalytic activity significantly.

While **11** was synthesized according to the procedure already established for **1**,[15] in the synthesis of the polymer-bound ligand chlorophosphite **10a** was used in excess. Loading of the resin was determined by gravimetry. Successful formation of the phosphoramidite is a prerequisite for catalytic activity and stereoselectivity. Thus, in the presence of hydroxymethyl polystyrene pretreated with Ac_2O or of a polystyrene resin to which a fully protected bispidine precursor had been attached, and which subsequently was treated with chlorophosphite **10a**, only very low conversion and no enantioselectivity was recorded. Finally, formation of the phosphoramidite was ascertained by treatment of the functionalized resin with TFA in methanol which resulted in release of 2,2′-dihydroxy-[1,1′]binaphthol (see the Experimental Section).

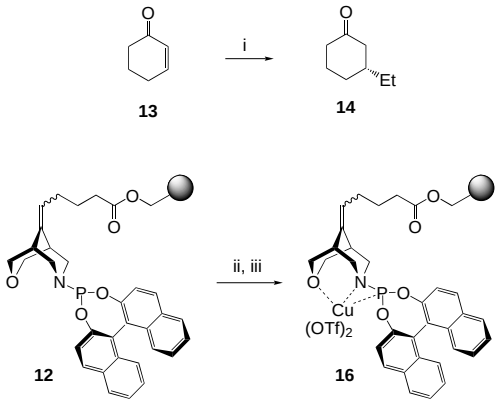
Alternatively, the desired polymer-bound phosphoramidite was formed by treatment of the immobilized N-deprotected oxabispidine with PCl_3 and subsequent reaction of the intermediary formed dichlorophosphine derivative with diol **15** (Scheme 5).



Scheme 5. Alternative synthesis of phosphoramidite **12**: i) TFA, CH_2Cl_2, 30 min; ii) Et_3N, CH_2Cl_2, 15 min; iii) PCl_3, Et_3N, THF, 1 h; iv) **15**, Et_3N, THF, 12 h.

The polymeric ligand systems synthesized by these different methods were then subjected to the enantioselective transformations described above. In the course of this investigation the loading of the resin was varied as well. Initial experiments employing toluene/CH_2Cl_2 mixtures (6:1) as solvent were only poorly reproducible. This finally was traced back to the fact that in this system both the immobilized ligand and $Cu(OTf)_2$ are insoluble leading to unreproducible catalyst formation. After substantial experimentation this problem was overcome by addtion of 3 vol % DMF to the solvent CH_2Cl_2 to solubilize $Cu(OTf)_2$ before exposure to the immobilized bispidine ligand. Treatment of the resin with such a solution (i.e., with an excess of $Cu(OTf)_2$) resulted in complete and reproducible loading of the polymer with the Cu salt, excess reagent was easily washed off. DMF is only a weak ligand for Cu^{II} and is readily replaced by stronger ligands like phosphoramidites.

Investigation of the different polymer catalysts prepared according to the methods detailed above, gave the results shown in Scheme 6 and Table 1. Gratifyingly, immobilization of the ligand and performing the reaction at $0\,^{\circ}C$ instead of $-30\,^{\circ}C$ (to ensure sufficient swelling of the polymer) resulted in only a minor drop of the enantioselectivity to 39 %. The method of preparation does not influence the performance of the catalyst. However, if the catalyst loading becomes too low, both yield and enantioselectivity decrease (compare entry 2 with entries 1, 3 and 4). Therefore, all further experiments were carried out employing resins with a loading of 0.52 mmol g^{-1}.



Scheme 6. Modified reaction conditions for the conjugate addition with ligand **12**/**16**: i) Et_2Zn, **16** toluene, CH_2Cl_2, $0\,^{\circ}C$, complete conversion 37–40 % *ee*; ii) 5 equiv $Cu(OTf)_2$, CH_2Cl_2/3 % DMF; iii) washing.

Table 1. Comparison of different solid phase oxa-bispidine ligands **12**/**16**.

Entry[a]	Loading/yield[b]	Mode of synthesis[c]	*ee* (conversion)[d]
1	0.52 mmol g^{-1}/71 %	CIP(BINOL) **10a**	39 % (complete)
2	0.40 mmol g^{-1}/27 %	CIP(BINOL) **10a**	37 % (complete)
3	1.11 mmol g^{-1}/76 %	CIP(BINOL) **10a**	40 % (86 %)
4	0.52 mmol g^{-1}/71 %	PCl_3, BINOL-OH **15**	40 % (complete)

[a] Addition of diethylzinc to cylohexen-2-one according to Scheme 7. [b] Loading/yield of two different resins with a maximum loading of 0.87 mmol g^{-1} and 1.46 mmol g^{-1}, respectively. [c] Either with the chlorophosphite reagent or with PCl_3 and 2,2′-dihydroxy-[1,1′]-binaphthyl, see text. [d] Determined by gas chromatographic analysis using a capillary column (Lipodex E, Macherey&Nagel), in all cases the (*R*) enantiomer was formed predominantly.

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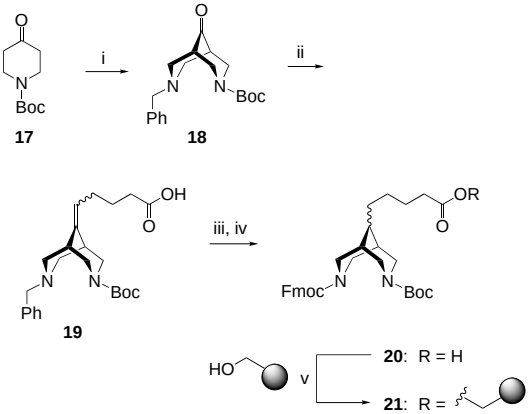
Synthesis of the library: For the synthesis of a bispidinone-phosphoramidite library a precursor for attachment to the solid support was required which carries two orthogonal protecting groups at the nitrogen atoms. This building block was generated by double Mannich reaction from **17** yielding bispidinone **18**, subsequent olefination of the ketone to give olefin **19** and exchange of the N-benzyl group for an Fmoc urethane (**20**) (Scheme 7). During hydrogenolytic removal of



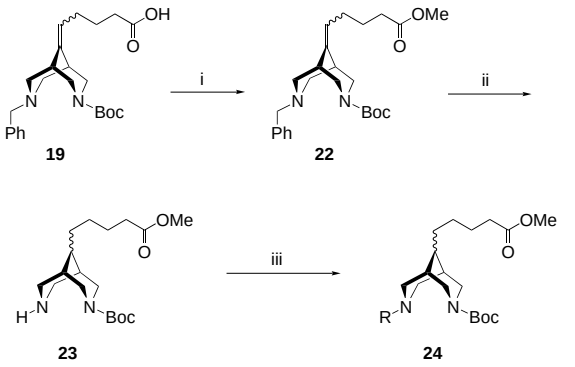
Scheme 7. Synthesis of bispidine **20** and coupling to the solid phase: i) $PhCH_2NH_2$, $(HCHO)_n$, AcOH, MeOH, 65 °C, 4 h, 81 %; ii) $BrPh_3P(CH_2)_4COOH$, KO*t*Bu, THF, 0 °C → RT, 2.5 h, 68 %; iii) H_2, Pd/C, EtOH, 12 h, RT, quant.; iv) FmocCl,$NaHCO_3$, THF, H_2O, 12 h, RT, 69 %; v) DIC, DMAP, CH_2Cl_2, 12 h, RT, 94 % (0.61 mmol g^{-1}).

the benzylamine the 9-*syn* and 9-a*nti* diastereomers are formed in a 1:1 ratio. Neither at this stage nor after Fmoc protection could their separation be achieved. Since the 9-substituent does not or only to a minor extent influence the stereoselection (see above) it appeared justified to employ the diastereomeric mixture for the library synthesis and evaluation.

Fmoc/Boc-protected bispidine carboxylic acid **20** was coupled to the solid support in high yield. Resin loading was determined gravimetrically and by means of UV-spectrometric quantification of the piperidine/fulvene adduct formed in the course of Fmoc removal.

Library synthesis on the solid support required that reliable methods for functionalization of the second nitrogen in the bispidine are available. These were established in solution for model compound **23** which was obtained from intermediate **19** after esterification and N-debenzylation (Scheme 8). Thus, methods for acylation, peralkylation, reductive amination, sulfonation and phosphorylation were established, including the choice of the right solvent system which should be homogeneous and allow for good swelling of the resin (see the Experimental Section for details). These were used for the analogous reactions on the solid phase.

After the methodical prerequisites had been established, the synthesis of the desired library was carried out. For this purpose, three different underlying structural frameworks were chosen, namely bispidine system **A1** embodying a phosphoramidite and a second nitrogen substituent to modulate the catalyst properties, hetero-bispidines **A2**–**A4** in which the modulating substituted nitrogen was replaced by an



Scheme 8. Model reactions with bispidine system **23**: i) EEDQ, MeOH, 12 h, RT, 75 %; ii) H_2, Pd/C, EtOH, 12 h, RT, 90 %; iii) various reactions and conditions.

oxygen, a sulfur or a carbon atom and piperidine system **A5** (Figure 1). Compounds **A2**–**A4** were only derivatized as phosphoramidites. As substituents of the modulating second nitrogen atom present in **A1** initially structural units **B1**–**B28** were chosen (Figure 2). These include aliphatic acyl groups (**B1**–**B4**), the Boc urethane (**B5**), urea and thiourea groups (**B6**, **B7**), aromatic acyl groups (**B8**–**B14**), aromatic substituted (**B15**, **B16**) and simple aliphatic (**B17**, **B18**) substituents, the permethylated amine (**B19**), sulfonamides (**B20**–**B24**) and phosphorus (**B25**–**B28**) substituents.

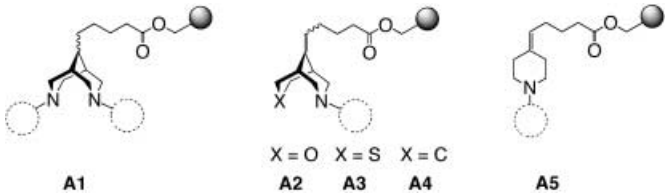


Figure 1. (Hetero-)bispidines **A1**–**A4** and piperidine **A5** as ligand backbones.

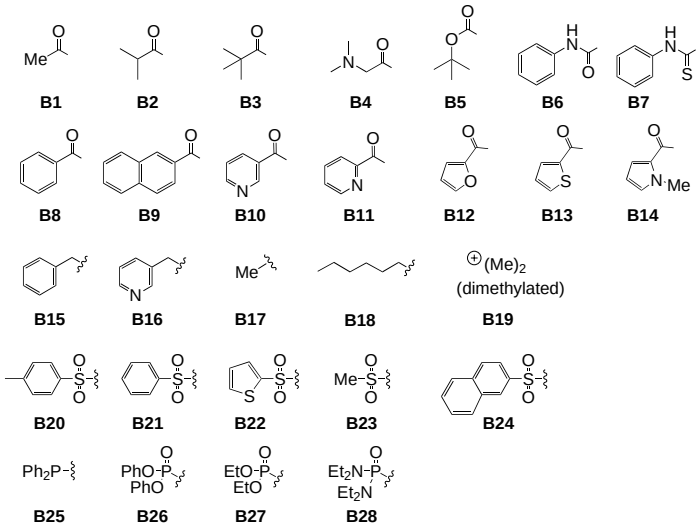


Figure 2. Building blocks for the ligand library: nitrogen substituents **B1**–**B28**.

0947-6539/02/0820-4770 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 20

The phosphoramidite structure was varied by introduction of different *ortho*-substituents into the binaphthyl groups (**C1**–**C4**, Figure 3) which were introduced by means of the corresponding chlorophosphites (**10a**–**d**).

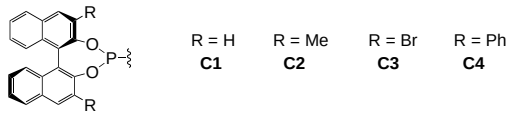
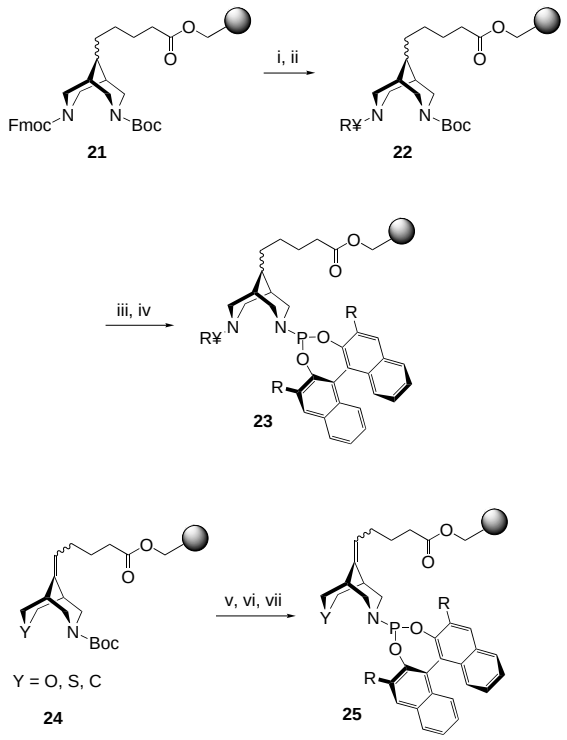


Figure 3. Building blocks for the ligand library: BINOL-phosphite groups **C1**–**C4**.

Library synthesis employing bispidine core **A1** was carried out by means of two successive deprotection/N-functionalization steps (Scheme 9). Thus, after removal of the Fmoc group from **21**, the nitrogen atom was derivatized by means of the



Scheme 9. Synthesis of solid phase ligands **23** and **25**: i) Piperidine; ii) modification at the N atom; iii) TFA, CH_2Cl_2, NEt_3; iv) ClP(R_2BINOL) Et_3N, toluene; v) TFA, CH_2Cl_2; vi) CH_2Cl_2, NEt_3; vii) ClP(R_2BINOL) Et_3N, toluene.

transformations described above to yield intermediates **22**. The Boc group was removed under acidic conditions, the secondary amine was liberated by treatment with NEt_3 and then the acid-labile phosphoramidites **23** were formed in the last step. For frameworks **A2**–**A4** embedded in **24** and by analogy for piperidine derivative **A5** the same Boc-deprotection/phosphitylation sequence was followed to give polymer-bound ligands **25** (Scheme 9).

Screening of the ligand library: The ligand library was synthesized and screened for enantioselective catalytic activity in two rounds of investigation. In the first round only frameworks **A1** were employed together with the underivated basic binaphthol phosphoramidite in order to find the best modulating nitrogen substituents. In the second step, the structure of the most promising candidates from step one was varied by introduction of differently substituted binaphthol units. This round also included hetero-substituted bispidine cores **A2**–**A4** and piperidine derivative **A5**.

After completion of the synthesis the ligands were converted to the corresponding polymer-bound copper complexes as described above and investigated in the Cu-catalyzed conjugate addition of $ZnEt_2$ to cyclohexenone at 0 °C. After the transformations had reached >95% conversion (2 h) the reactions were quenched with 2 N HCl and the enantiomeric ratio was determined without further separation procedures by means of gas chromatography, employing a chiral stationary phase.

The results of the first round of investigation are displayed in Figure 5, see below. It is clearly visible that the nature of the second nitrogen has a profound influence on the efficiency of the stereoselection.

Thus, in the presence of sterically demanding acyl-substituents such as the isobutyryl (**B2**, 39% *ee*) and, in particular, the pivaloyl group (**B3**, 44% *ee*) asymmetric induction is high. An acetamide (**B1**, 11% *ee*), a Boc group (**B5**, 29% *ee*), the urea and thiourea groups (**B6**, **B7**) (35 and 27%) are less advantageous. Among the aromatic amides, weakly complexing functional groups such as the thiophene group (**B13**, 38% *ee*) were much better than nitrogen heterocycles or the unfunctionalized benzamide **B8** (23% *ee*). Pyridine heterocycles give particularly low *ee* values probably due to their ability to from Cu^{II} complexes. A similar trend is visible for **B15** (35% *ee*) and **B16** (21% *ee*) incorporating an N-benzyl-and a 3-pyridylmethyl group, respectively. In the presence of aliphatic amines (**B17**, **B18**) the enantioselectivity is low. Permethylation (**B19**, 29% *ee*) and generation of an aminophosphine were also less advantageous. Remarkably, toluene sulfonamide **B20** (56% *ee*) and benzene sulfonamide (**B21**, 51% *ee*) gave the highest *ee* value as determined in the first screening round; other sulfonamides (**B22**–**B24**, 19–33% *ee*) were less advantageous. The diphenyl phosphoric amide **B26** (50% *ee*) gave the highest *ee* value of the phosphorous substituents (**B25**–**B28**, 37–41% *ee*) in the first screening round.

In order to determine, if the introduction of stereogenic centres into the N-substituent would give rise to higher stereoselectivity, the bispidine core (**A1**) carrying the basic binaphthol substituent (**C1**) was combined with N-acetylated (**D1**) or N-sulfonylated (**D2**–**D4**) amino acids (**AA1**–**AA7**) or dipeptides (**AA1/2**–**AA3**) (Figure 4). The synthesis of the polymer-bound ligands followed the route described above. However, evaluation of these ligands in the conjugate addition to cyclohexenone showed that the chiral N-substituents did not exert a positive effect (Figure 6). Thus, in the presence of an acetylated or sulfonylated amino acid, the *ee* value in most cases remained below the 30% line. For dipeptide substituents even the 20% value was reached in only one case.

Based on these results ligands **B3**, **B13**, **B20** and **B26** embodying the most promising N-substituents were subjected

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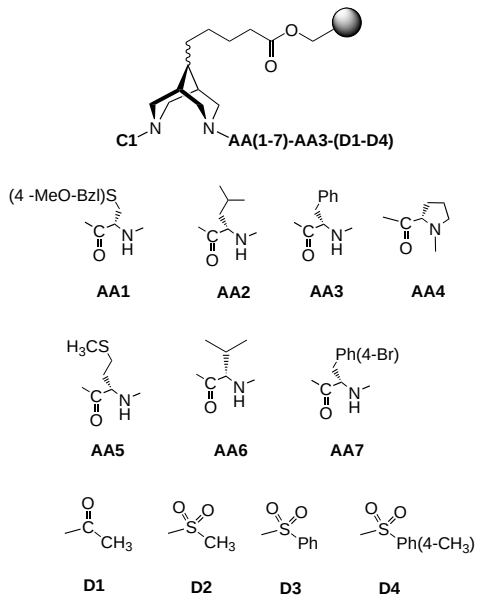


Figure 4. Amino acid and dipeptide substituted ligands.

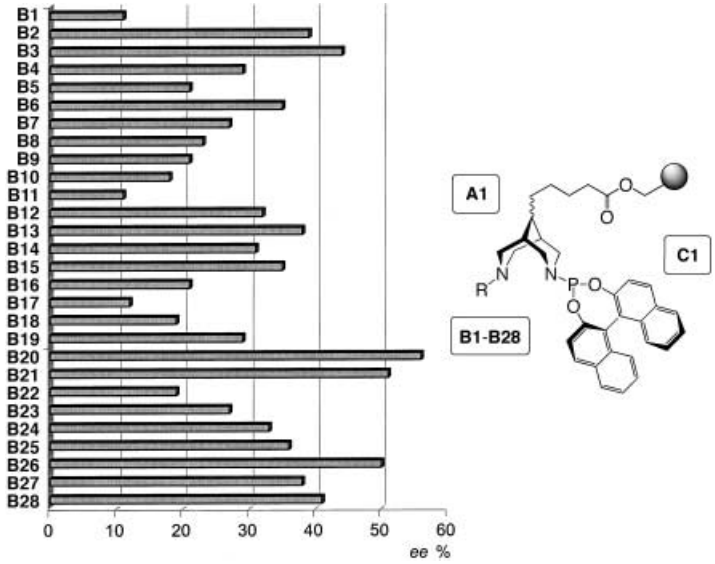


Figure 5. *ee* Values determined with ligand combinations **A1-B(1–28)-C1**.

to a second round of investigation in which the structure of the binaphthol system was varied (**C1**–**C4**). This second round also included the bispidine analogues **A2**–**A5**. The results of the corresponding enantioselective conjugate addition reactions are shown in Figure 7.

Several trends are apparent from these reactions. First, for the pivaloyl amide (**A1-B3-C1/C2**) raising the steric demand of the binaphthyl substituent from H to CH_3 led to significant improvement of the enantioselectivity from 44 to 67% *ee*. This is the highest value recorded in this study. However, the selectivity was lower in the presence of a bromo- or phenyl substituent.

A similar oberservation is made for the thiophenoylamide, for which the *ee* raises from 38% (**A1-B13-C1**) to 54% (**A1-B13-C2**) if a methyl group is introduced, but in the presence of a bromine or a phenyl group it is lower again (**A1-B13-C3/4**). Interestingly, this trend is reversed for compounds embodying a toluene sulfonamide (**A1-B20-C1/2**) and a diphenyl-phosphorylamide (**A1-B26-C1/2**). In both cases the *ee* value was lower, if a sterically more demanding methyl substituent was introduced into the binaphthol residue.

In the presence of hetero-substituted bispidine analogues **A2**–**A4**, and if piperidine building block **A5** was introduced, the enantioselectivity did not reach the highest values determined for the most efficient combination in the bispidine system **A1**. Strikingly, this substituted analogue **A3** was the least advantageous ligand. In its presence the polymer turned green, indicating strong complexation of the copper. This is in accordance with the finding of the pyridine-containing ligand discussed above.

The results shown in Figures 5–7 show that the two substituents attached to the underlying bispidine core display cooperative effects. But these effects are not necessarily additive in each combination within the bispidine system studied here. A positive influence of a substituent determined through varying ligand structure at one position while keeping the other unchanged does not necessarily remain when the second group is varied.

Therefore, the most advantageous modulating N-substituent identified in the first screening round, that is the 4-tosyl

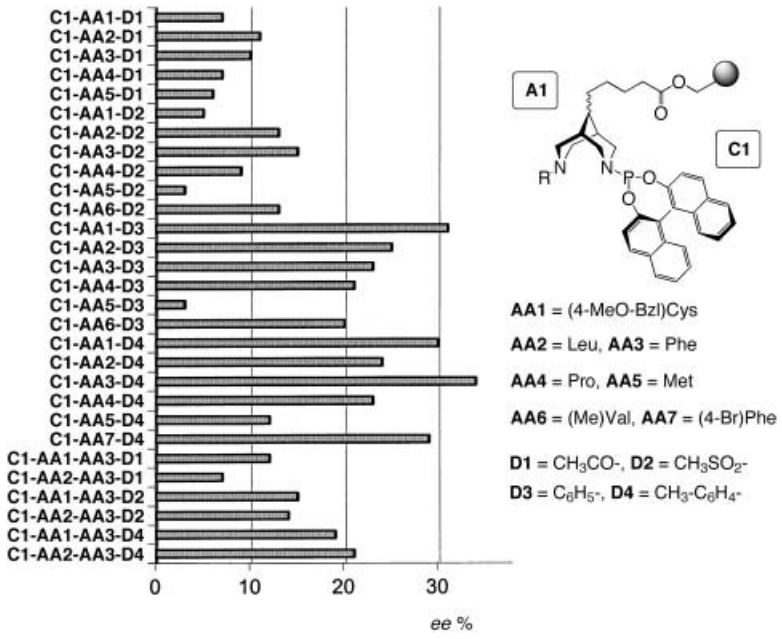


Figure 6. *ee* Values determined with amino acid ligands incorporating substituted amino acids or dipeptides.

0947-6539/02/0820-4772 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 20

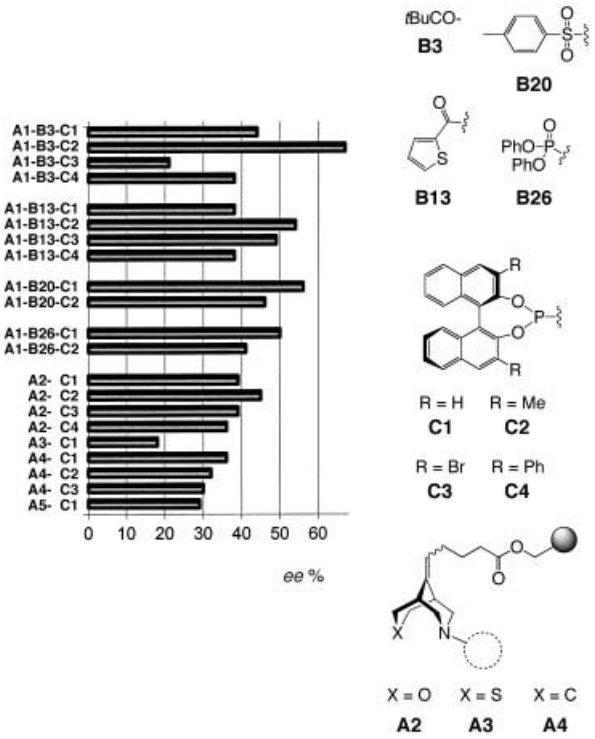
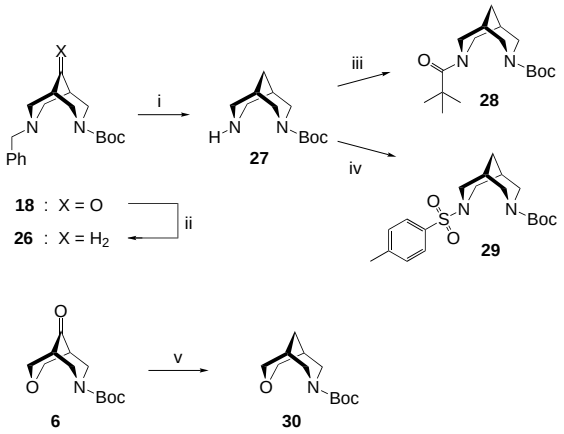


Figure 7. *ee* Values determined with ligand combinations **Ax-Bx-C(1–4)**.

group **B20** did not emerge as the substituent of choice after the second round. Rather, the pivaloyl amide **B3** which reached only rank four in the first round turned out to be most advantageous after appropriate combination with the right binaphthyl unit. Thus, if we had followed the frequently used strategy of "positional scanning"[2, 25] optimizing each substituent independently and subsequently carrying only the best candidate through (instead of several ones as done here), the most efficient ligand **A1-B3-C2** would not have been identified. This finding is of general relevance to combinatorial ligand and catalyst development. It shows that the concept of "positional scanning" may not be general and should be applied with care.

Solution-phase validation of the screening results: In order to validate the screening of the solid phase bound ligands and to prove the concept of ligand optimization on the solid support, four soluble ligands were synthesized and the results obtained in homogeneous solution were compared with the values determined for the transformations in the presence of the same ligands immobilized on the solid support. To this end, *N*-tosyl-*N*′-binaphthyl ligand **31** as well as *N*-pivaloyl- and *N*-tosyl-*N*′-*ortho*-methylbinaphthyl ligands **32** and **33**, and oxa-*N*-*ortho*-methylbinaphthyl bispidine **34** were synthesized as shown in Schemes 10 and 11.

Boc-/benzyl-protected bispidinone **18** was deoxygenated to give bispidine **26** by conversion into the tosylhydrazone and subsequent treatment with $NaCNBH_3$.[25] After hydrogenolytic removal of the N-benzyl protecting group monoprotected bispidine **26** was obtained, which was converted without isolation and in high yield into pivalic acid amide **28** and toluene-sulfonamide **29** (Scheme 10). By analogy Boc-masked oxa-bispidine **30** was synthesized from ketone **6**.

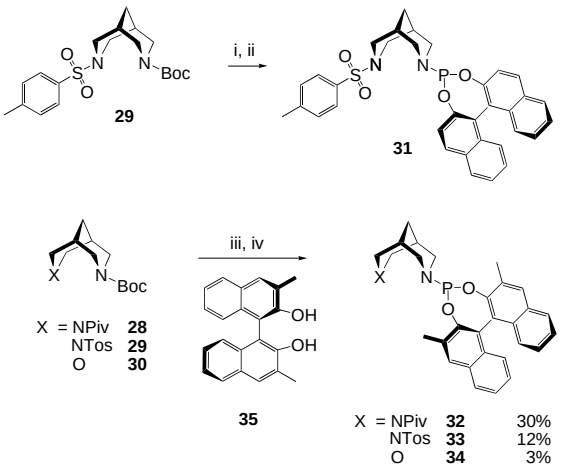


Scheme 10. Synthesis of Boc-protected (hetero-)bispidines **28**, **29** and **30**: i) H_2, Pd/C, EtOH, 12 h, RT; ii) $TosNHNH_2$, TosOH, $NaCNBH_3$, DMF, 2 h, 100 °C, 43 %; iii) Piv_2O, DMAP, pyridine, 12 h, RT, 71 %; iv) TosCl, DMAP, pyridine 12 h, RT, 72 % (two steps); v) $TosNHNH_2$, TosOH, $NaCNBH_3$, DMF, 2 h, 100 °C, 48 %.

The Boc group was removed from **28**–**30** by treatment with TFA and the liberated amines were then converted into the desired phosphoramidites employing the method for phosphoramidite formation with chlorophosphite **10a** and product isolation developed earlier.[15] However, this procedure was only practical for ligand **31** which embodies an underivatized binaphthyl substituent.

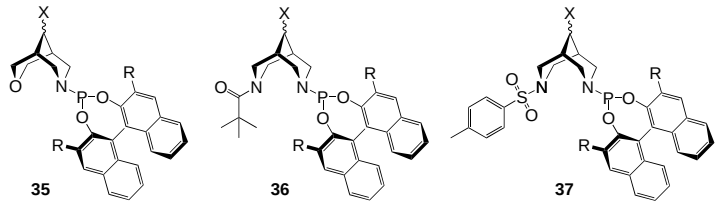
If chlorophosphite **10b** carrying *ortho*-methyl-substituted binaphthol was used in 1.5-fold excess, only traces of the desired products were isolated. Obviously, the steric demand of the methyl groups prevent efficient product formation.[27] Utilization of a large excess of chlorophosphite as in the generation of the polymer-bound ligand resulted in contamination of the products with the binaphthol after chromatographic separation employing Florisil as the stationary phase.

The synthesis of **30**–**32** could be achieved by treatment of the amines obtained from **28**–**30** with PCl_3 first and subsequent coupling of the resulting dichlorophosphoric acid amides with *ortho*-methyl-substituted binaphthol **35** accord-



Scheme 11. Synthesis of phosphoramidites **31**–**34**: i) TFA, CH_2Cl_2, 30 min, RT; ii) ClP(BINOL), **10a**, Et_3N, toluene, 12 h, RT, 51 %; iii) TFA, CH_2Cl_2, 30 min, RT; iv) PCl_3, Et_3N, THF, 1 h, 0 °C, then **35**, Et_3N, THF, 12 h, RT.

Table 2. Comparison of polymer supported ligands with the corresponding soluble ligands.



Entry[a]	Ligand group	BINOL substitution	Heterogenous *ee*[b] [%] (ligand)	homogenous *ee*[b] [%] (ligand)
1	oxa- (**35**)	H	39 (**A2-C1**)	43 (**1**)
2		Me	45 (**A2-C2**)	47 (**34**)[c]
3	pivaloyl- (**36**)	H	44 (**A1-B3-C1**)	n.d.
4		Me	67 (**A1-B3-C2**)	64 (**32**)
5	toluene-4-sulfonyl- (**37**)	H	56 (**A1-B20-C1**)	56 (**31**)
6		Me	46 (**A1-B20-C2**)	51 (**33**)

[a] Addition of diethylzinc to cylohexen-2-one according to Scheme 6 using resins with 0.5 – 0.6 mmol g^{-1} loading or according to Scheme 4 with soluble ligands at 0 °C. [b] Determined by gas chromatographic analysis using a capillary column (Lipodex E, Macherey&Nagel), in all cases the (*R*) enantiomer was formed predominantly. [c] Using 1 mol% ligand.

ing to the alternative procedure for phosphoramidite formation described above (see Scheme 5). Although yields were low, phosphoramidites **32** – **34** were available in sufficient amounts for further investigation as stereodirecting ligands.

The results obtained in the Cu-catalyzed conjugate addition of $ZnEt_2$ to cyclohexenone are given in Table 2 and compared with the results observed for the immobilized ligands. In all cases, the results for the homogeneously catalyzed reactions very similar to the heterogeneous transformations and also the trends gleaned from the ligand screening are correctly mirrored.

Thus, for the oxa-bispidine system (entries 1 and 2) the *ee* is slightly higher in both cases if the *ortho*-methyl substituted binaphthol is present, and the *ee* values are very similar.

The pivalic acid amide was also the best ligand in the homogeneously catalyzed transformations, with a slightly lower *ee* value (entry 4).

Also, the observation that an *ortho*-methyl group in the binaphthol substituent leads to a reduction of the enantioselectivity is recorded in the homogeneous case, and once more the *ee* values are fairly similar (entries 5 and 6).

Conclusion

We have successfully established a method for the combinatorial development of chiral ligands for Cu-catalyzed enantioselective conjugate addition reactions to enones. An important feature of this method is that ligand optimization on the solid phase correctly mirrors the results obtained with the analogous ligands in homogeneous solution. In addition, ligand generation on the solid support in this case was much more advantageous than the synthesis and isolation of the soluble ligands. Thus, in the case described here the use of the immobilized ligands appears to be more advantageous. This is the first case of a development and successful use of chiral polymer-bound ligands for enantioselective Cu-catalyzed conjugate addition reactions.

Our study provides a convincing example for the validity of the concept that ligand optimization for asymmetric catalysis by means of combinatorial and solid-phase chemistry is feasible and efficient. By means of the developed methodology a library of 78 ligands was readily synthesized and screened for performance.

In the screening reported herein, *ee* values ranging from 3% to 67% were determined; the best ligand showed much better enantioselectivity than the oxa-bispidine phosphoramidite which served as guiding structure for library development.

These results open up and indicate the application of our approach to much broader ligand development both for conjugate addition reactions and the use of phosphoramidite ligands in other enantioselective transformations.

Experimental Section

General remarks: Melting points were determined in open capillaries using a Büchi 540 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC250, AM400, DRX500, or Varian Mercury400 spectrometer at room temperature. IR spectra were recorded on a Bruker IFS88 spectrometer. Mass spectra, high-resolution mass spectra (HRMS) and fast-atom-bombardement mass spectra (FAB) were measured on a Finnigan MAT MS70 spectrometer. Specific optical rotation values were determined with a Perkin – Elmer polarimeter 341. For gas chromatography a Hewlett – Packard 5890 Series II gas chromatograph with FID detector and a capillary column FS Lipodex E (Macherey – Nagel) was used.

Bispidines with N-acyl groups show splitting of all signals in NMR. This phenomenon was already described in the literature[28] and is due to the hindered rotation of the nitrogen substituents.

Solvents were dried by standard methods and used immediately or stored over molecular sieves. For column chromatography silica gel (40 – 64 μm, Baker or Fluka) or Florisil (Fluka) were used. Commercial reagents were used without further purification except for PCl_3 which was distilled. (*R*)-1,1′-Binaphthyl-2,2′-diol was purchased from Merck and diethylzinc (1.1M

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in toluene) was purchased from Fluka. Pd/C (10%) was donated by Degussa AG.

Disubstituted 2,2′-dihydroxy-[1,1′]-binaphthyls[27, 30] were prepared according to literature methods.

7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (5):[5, 22] A solution of tetrahydropyran-4-one (0.92 mL, 5.0 mmol), benzylamine (1.11 g, 10.3 mmol) and acetic acid (0.57 mL, 10.0 mmol) in dry methanol (20 mL) was added over a period of 1 hto a suspension of coarse-grained paraformaldehyde (0.66 g, 22.1 mmol) in dry methanol (20 mL) at 65 °C. Another portion of paraformaldehyde (0.66 g, 22.1 mmol) was added and the mixture was stirred for 1 h at 65 °C. After cooling water (200 mL) and 1N KOH solution (10 mL) were added, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate 2:1) to yield an oil (1.74 g, 7.52 mmol, 75%) {ref. [22]: 39%}. $R_f = 0.37$ (*n*-hexane/ethyl acetate 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.36-7.24$ (m, 5H; arom. H), 4.22 (d, $J = 11$ Hz, 2H; $CH_{2eq}O$), 3.89 (dd, $J = 11$ Hz, $J = 3$ Hz, $CH_{2ax}O$), 3.57 (s, 2H; CH_2Ph), 3.13 (dd, $J = 11.5$ Hz, $J = 3$ Hz $CH_{2eq}N$), 2.95 (dd, $J = 11.5$ Hz, $J = 6$ Hz, $CH_{2ax}N$), 2.53 (br, 2H; CH).

7-(*tert*-Butyloxycarbonyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (6): 1-Chloroethylchloroformate (306 μL, 2.81 mmol) was added at 0 °C to a solution of bispidinone **5** (500 mg, 2.16 mmol) in CH_2Cl_2 (20 mL). After slowly warming to room temperature the mixture was refluxed for 2 h. All volatiles were removed in vacuo and the resulting oil was taken up in methanol (20 mL) and refluxed for 1 h. The solvent was evaporated and the solid residue was taken up in 1N KOH solution (10 mL) and dioxane (10 mL). To this mixture was added Boc_2O (708 mg, 3.24 mmol) and it was stirred overnight. The mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 2:1) to yield a solid (456 mg, 1.89 mmol, 87%). M.p. 86–87 °C; $R_f = 0.35$ (cyclohexane/ethyl acetate 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 4.83$ (d, $J = 14$ Hz, 1H; $CH_{2eq}N$), 4.62 (d, $J = 14$ Hz, 1H; $CH_{2eq}N$), 4.41 (d, $J = 11$ Hz, 1H; $CH_{2eq}O$), 4.34 (d, $J = 11$ Hz, 1H; $CH_{2eq}O$), 3.93 (d, $J = 11$ Hz, 1H; $CH_{2ax}O$), 3.88 (d, $J = 11$ Hz, 1H; $CH_{2ax}O$), 3.35 (d, $J = 14$ Hz, 1H; $CH_{2ax}N$), 3.22 (d, $J = 14$ Hz, 1H; $CH_{2ax}N$), 2.39 (s, 1H; CH), 2.35 (s, 1H; CH), 1.50 (s, 9H; $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 210.9$ (CHC=O), 155.3 (C=O urethane), 80.5 ($C(CH_3)_3$), 74.2, 74.2 (CH_2O), 50.7 (CH_2N), 50.6, 50.3 (CH), 49.9 (CH_2N), 28.6 ($(CH_3)_3C$); IR (KBr): $\tilde{\nu} = 2856$ (Bohlmann-band),[29] 1738, 1671 (C=O); MS (EI, 70 eV): *m*/*z* (%): 241 (40) $[M]^+$, 185 (35) $[M - t\text{Bu}]^+$, 141 (20) $[M - \text{Boc}]^+$; HRMS (EI, 70 eV): calcd for $C_{12}H_{19}NO_4$: 241.1314, found: 241.1314.

7-(*tert*-Butyloxycarbonyl)-9-(4′-carboxybutylidene)-3-oxa-7-azabicyclo[3.3.1]nonane (7): Potassium-*tert*-butoxide (837 mg, 7.46 mmol) was added in portions at 0 °C to a suspension of (4-carboxybutyl)-triphenylphosphonium bromide (1.65 g, 3.73 mmol) in THF (30 mL). The suspension was warmed to room temperature and stirred for 30 min. After cooling to 0 °C a solution of bispidinone **6** (300 mg, 1.24 mmol) in THF (10 mL) was added slowly. The mixture was warmed to room temperature slowly and stirred for 2 h. The suspension was poured on sat. NH_4Cl solution (100 mL) and extracted with chloroform (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (chloroform/methanol 1%, then 2%) to yield an oil (293 mg, 0.90 mmol, 72%). $R_f =$ 0.30 (chloroform/methanol 3%); ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of isomers): $\delta = 5.27$, 5.26 (t, $J = 7$ Hz, 1H (isomers); CH=), 4.47 (t, $J = 13$ Hz, 1H; $CH_{2eq}N$), 4.30 (t, $J = 11$ Hz, 1H; $CH_{2eq}N$), 4.14 (dd, $J = 10$ Hz, $J = 7$ Hz, 1H; $CH_{2eq}O$), 4.07 (dd, $J = 10$ Hz, $J = 4$ Hz, 1H; $CH_{2eq}O$), 3.70–3.58 (m, 2H; $CH_{2ax}O$), 3.09 (m, 1H; $CH_{2ax}N$), 2.99 (m, 1H; $CH_{2ax}N$), 2.54 (m, 1H; $CHCH_2O$), 2.36 (t, $J = 7$ Hz, 2H; CH_2COOH), 2.12–2.06 (m, 3H; $CHCH_2O$, CH_2CH_2COOH), 1.71 (dt, $J = 7$ Hz, 2H; CH_2CH=), 1.47 (s, 9H; $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 100.6 MHz, mixture of isomers): $\delta =$ 178.7, 178.6 (COOH), 155.6, 155.55 (C=O urethane), 139.6 (*C*=CH), 118.9 (*C*H=C), 79.8 ($C(CH_3)_3$), 74.3, 74.2, 73.5, 73.4 (CH_2O), 51.1, 50.4, 50.1, 49.4 (CH_2N), 42.3, 42.2, 35.6, 35.4 (*C*HC=), 33.5 (CH_2COOH), 28.7 ($(CH_3)_3C$), 25.9 (CH_2CH=), 25.2 (CH_2CH_2COOH); IR (KBr): $\tilde{\nu} = 2851$ (Bohlmann-band),[29] 1694 cm^{-1} (C=O); MS (FAB, glycerol): *m*/*z* (%): 326 (5) $[M+H]^+$, 226 (45) $[M - \text{Boc}+H]^+$; HRMS (FAB, glycerol): calcd for $C_{17}H_{28}NO_5$: 326.1967, found: 326.1951.

7-(*tert*-Butyloxycarbonyl)-9-(4′-methoxycarbonylbutylidene)-3-oxa-7-azabicyclo[3.3.1]-nonane (8): EEDQ (236 mg, 0.95 mmol) was added to a solution of carboxylic acid **7** (259 mg, 0.80 mmol) in methanol (8 mL) and the mixture was stirred at room temperature overnight. After evaporation of the solvent in vacuo the residue was taken up in ethyl acetate (10 mL) and extracted with 1N HCl (3 × 5 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 5:2 to yield an oil (221 mg, 0.65 mmol, 82%). $R_f = 0.38$ (cyclohexane/ethyl acetate 5:2); ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of isomers): $\delta = 5.26$, 5.25 (t, $J =$ 7 Hz, 1H (isomers); CH=), 4.48 (t, $J = 13$ Hz, 1H; $CH_{2eq}N$), 4.31 (dd, $J =$ 13 Hz, $J = 8$ Hz, 1H; $CH_{2eq}N$), 4.13 (t, $J = 9$ Hz, 1H; $CH_{2eq}O$), 4.07 (dd, $J =$ 11 Hz, $J = 5$ Hz, 1H; $CH_{2eq}O$), 3.70–3.58 (m, 2H; $CH_{2ax}O$), 3.67 (s, 3H; CH_3OCO), 3.08 (t, $J = 13$ Hz, 1H; $CH_{2ax}N$), 2.98 (m, 1H; $CH_{2ax}N$), 2.53 (m, 1H; $CHCH_2O$), 2.33 (t, $J = 7$ Hz, 2H; CH_2COO), 2.12–2.03 (m, 3H; $CHCH_2O$, CH_2CH_2COO), 1.71 (dt, $J = 8$ Hz, 2H; CH_2CH=), 1.47 (s, 9H; $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 100.6 MHz, mixture of isomers): $\delta = 174.1$ ($COOCH_3$), 155.5, 155.4 (C=O urethane), 139.70, 139.67 (*C*=CH), 118.9, 118.8 (*C*H=C), 79.5 ($C(CH_3)_3$), 74.31, 74.25, 73.5, 73.4 (CH_2O), 51.7 (CH_3OCO), 51.1, 50.4, 50.2, 49.4 (CH_2N), 42.4, 42.3, 35.6, 35.5 (*C*HC=), 33.5, 33.4 (CH_2COO), 28.7 ($(CH_3)_3C$), 26.0 (CH_2CH=), 25.4 (CH_2CH_2COO); IR (KBr): $\tilde{\nu} = 2849$ (Bohlmann-band),[29] 1738, 1694 cm^{-1} (C=O); MS (FAB, 3-NBA): *m*/*z* (%): 340 (20) $[M+H]^+$, 338 (15) $[M - H]^+$, 240 (100) $[M - t\text{Bu}+H]^+$, 238 (45) $[M - t\text{Bu} - H]^+$; HRMS (FAB, 3-NBA): calcd for $C_{18}H_{30}NO_5$: 340.2124, found: 340.2150.

9-(4′-Methoxycarbonylbutylidene)-3-oxa-7-azabicyclo[3.3.1]nonane-7-[(*R*)-binaphthyl-2,2′-diyl]phosphite (11): Trifluoroacetic acid (1 mL) was added to a solution of Boc-bispidine derivative **8** (108 mg, 0.32 mmol) in CH_2Cl_2 (1 mL) and the solution was stirred at room temperature for 30 min. After evaporation of the solvent and additional coevaporation with toluene the residue was dissolved in toluene (3 mL) and treated with triethylamine (400 μL, 2.9 mmol). To this solution was added dropwise a solution of (*R*)-[binaphthyl-2,2′-diyl]-chlorophosphite **10** (151 mg, 0.43 mmol) in toluene (1 mL) at room temperature and the mixture was stirred overnight at 80 °C. The mixture was filtered and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on Florisil (pre-treated with triethylamine; cyclohexane/CH_2Cl_2 2:1, 2% Et_3N) to yield a mixture of diastereomers as a solid (72 mg, 0.13 mmol, 41%). M.p. 105–106 °C; $R_f = 0.9$ (CH_2Cl_2/Et_3N 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of diastereomers): $\delta = 7.96$ (d, $J = 9$ Hz, 1H; arom. H), 7.92–7.87 (m, 3H; arom. H), 7.56 (dd, $J = 9$ Hz, $J = 3$ Hz, 1H; arom. H), 7.44–7.33 (m, 5H; arom. H), 7.30–7.22 (m, 2H; arom. H), 5.22, 5.17 (t, $J = 3$ Hz, 1H (isomers); CH=), 4.08 (d, $J = 10$ Hz, 1H; $CH_{2eq}O$), 3.99 (t, $J = 10$ Hz, 1H; $CH_{2eq}O$), 3.76–3.45 (m, 5H; $CH_{2ax}O$, $CH_2N(3)$), 3.67, 3.64 (s, 3H (isomers); CH_3OCO), 3.28–3.19 (m, 1H; CH_2N), 2.57–2.51 (m, 1H; $CHCH_2O$), 2.33, 2.30 (t, $J = 8$ Hz, 2H (isomers); CH_2COO), 2.11–2.08 (m, 1H; $CHCH_2O$), 2.05, 1.98 (dt, $J =$ 7 Hz, 2H (isomers); CH_2CH_2COO), 1.74–1.63 (m, 2H; CH_2CH=); ^{13}C NMR ($CDCl_3$, 100.6 MHz, mixture of diastereomers): $\delta = 174.1$ ($COOCH_3$), 148.4, 148.3, 147.3, 147.2 (arom. C), 138.7 (*C*=CH), 132.54, 132.47, 132.0, 131.6 (arom. C), 131.4, 131.0, 128.7, 127.5, 127.2, 126.9, 126.8, 125.8, 125.7 (arom. CH), 123.9, 123.5 (arom. C), 121.6, 121.5 (arom. CH), 119.9, 119.8 (*C*H=C), 73.7, 73.6, 72.9, 72.8 (CH_2O), 52.1 (CH_2N), 51.8 (CH_3OCO), 51.5, 50.8, 50.7 (CH_2N), 42.0, 35.3, 35.2 (*C*HC=), 33.51, 33.49 (CH_2COO), 26.0 (CH_2CH=), 25.36, 25.32 (CH_2CH_2COO); ^{31}P NMR ($CDCl_3$, 202.5 MHz): $\delta = 148.5$; IR (KBr): $\tilde{\nu} = 2852$ (Bohlmann-band),[29] 1736 cm^{-1} (C=O); MS (FAB, 3-NBA): *m*/*z* (%): 554 (90) $[M+H]^+$, 315 (35) $[PBINOL]^+$, 240 (10) $[M - PBINOL+H]^+$; HRMS (FAB, 3-NBA): *m*/*z* (%): calcd for $C_{33}H_{32}NO_5P$: 554.2096, found: 554.2075.

General procedure for the synthesis of the (3,3′-disubstituted) (*R*)-[binaphthyl-2,2′-diyl]-chlorophosphite 10a–d:[24] A solution of (3,3′-disubstituted) 2,2′-dihydroxy-[1,1′]-binaphthyl[27, 30] in THF was added over a period of 30 min to a solution of PCl_3 (1.3 equiv) and triethylamine (2.05 equiv) in THF. The mixture was stirred at room temperature for 90 min. The precipitate was filtered off under argon and the solvent was evaporated in vacuo. The residue was taken up in diethyl ether and filtered again under argon. The solvent was evaporated in vacuo. The remaining voluminous solid was obtained in almost quantitative yield and was used in coupling procedures with bispidines without further purification.

Proof of the formation of the phosphoramidites by cleavage from the solid support: A solution of methanol (0.5 mL), trifluoroacetic acid (0.1 mL) and CH_2Cl_2 (2 mL) was added to the phosphoramidite resin **12** (53 mg,

0.52 mmol g^{-1}, 0.028 mmol) in a syringe reactor. The mixture was shaken for 1 h. The liquid phase was separated and the resin was washed with CH_2Cl_2 (2 ×). The combined organic layers were evaporated in vacuo to yield a colourless solid, 2,2′-dihydroxy-[1,1′]-binaphthyl (7.7 mg (0.027 mmol, 98 %). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.98$ (d, $J = 11$ Hz, 2H; arom. H), 7.90 (d, $J = 11$ Hz, 2H; arom. H), 7.40 – 7.28 (m, 6H; arom. H), 7.16 (d, $J = 10$ Hz, 2H; arom. H), 4.83 (br s, 2H; OH).

Addition of diethylzinc to cyclohexen-2-one with soluble ligands, 3-ethylcyclohexanone: The phosphoramidite ligand (0.033 mmol) was added as a solid to a suspension of copper(II)trifluoromethanesulfonate (11 mg, 0.030 mmol) in a mixture of toluene/CH_2Cl_2 (3.5 mL, 6:1). The mixture was stirred for 1 h at room temperature and cooled to the indicated temperature. Then cyclohexen-2-one (96 μL, 1.0 mmol) and diethylzinc (1.2 mL, 1M solution in toluene, 1.2 mmol) were added. The yellow, heterogeneous reaction mixture was stirred for 2 h at the indicated temperature. Then 1N HCl (5 mL) was added and the mixture was stirred for 30 min thoroughly. The mixture was extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo with caution. The residue was chromatographed on silica gel with pentane/diethyl ether and the product was obtained as a colourless liquid.

The results with ligand **8** and ligand **32** are given as representative examples.

a) with ligand **8**: Yield: 95 %, 46 % *ee*, (*R*)-enantiomer predominating, $[\alpha]_D^{20} = +10.6$ ($c = 1.5$, $CHCl_3$), {ref. [31]: positive for (*R*)-enantiomer}.

b) with ligand **32**: Yield: 96 %, 64 % *ee*, (*R*)-enantiomer predominating, $[\alpha]_D^{20} = +12.5$ ($c = 1.0$, $CHCl_3$), {ref. [31]: positive for (*R*)-enantiomer}.

General data: $R_f = 0.35$ (pentane/diethyl ether 7:1); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 2.48 – 2.18$ (m, 3H), 2.12 – 1.85 (m, 3H), 1.76 – 1.55 (m, 2H), 1.43 – 1.26 (m, 3H), 0.91 (t, $^3J = 9$ Hz, 3H, CH_3); GC (100 °C, isothermal): $t_R = 16.7$ min [(*R*)-enantiomer], $t_R = 17.4$ min [(*S*)-enantiomer].

3-(*tert*-Butyloxycarbonyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonan-9-one (18): A solution of 1-Boc-piperidin-4-one (2.00 g, 10.0 mmol), benzylamine (1.11 g, 10.3 mmol) and acetic acid (0.57 mL, 10.0 mmol) in dry methanol (50 mL) was added dropwise over a period of 1 h at 65 °C to a suspension of coarse-grained paraformaldehyde (0.66 g, 22.1 mmol) in dry methanol (40 mL). Another portion of paraformaldehyde (0.66 g, 22.1 mmol) was added and the mixture was stirred for 1 h at 65 °C. After cooling water (400 mL) and 1N KOH solution (20 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate 3:1) to yield an oil (2.63 g, 7.96 mmol, 79 %). $R_f = 0.35$ (*n*-hexane/ethyl acetate 3:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.35 – 7.24$ (m, 5H; arom. H), 4.58 (d, $J = 13$ Hz, 1H; $CH_{2eq}N(3)$), 4.41 (d, $J = 13$ Hz, 1H; $CH_{2eq}N(3)$), 3.54 (d, $J = 13$ Hz, 1H; NCH_2Ph), 3.48 (d, $J = 13$ Hz, 1H; NCH_2Ph), 3.36 (d, $J = 13$ Hz, 1H; $CH_{2ax}N(3)$), 3.28 (d, $J = 13$ Hz, 1H; $CH_{2ax}N(3)$), 3.19 (d, $J = 11$ Hz, 1H; $CH_{2eq}N(7)$), 3.15 (d, $J = 11$ Hz, 1H; $CH_{2eq}N(7)$), 2.72 (d, $J = 10$ Hz, 1H; $CH_{2ax}N(7)$), 2.66 (d, $J = 10$ Hz, 1H; $CH_{2ax}N(7)$), 2.44 (s, 3H; $CHCH_2N$), 2.40 (s, 3H; $CHCH_2N$), 1.54 (s, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 213.5$ ($CHC{=}O$), 154.7 (C=O urethan), 137.4 (arom. C), 128.7, 128.3, 127.2 (arom. CH), 80.0 ($C(CH_3)_3$), 61.8 (CH_2Ph), 59.0, 58.7 ($CH_2N(7)$), 50.5, 49.8 ($CH_2N(3)$), 47.6 ($CHC{=}O$), 28.6 ($(CH_3)_3C$); IR (drift): $\tilde{\nu} = 2801$ (Bohlmann-band),[29] 1734, 1695 cm^{-1} (C=O); MS (FAB, 3-NBA): *m*/*z* (%): 331 (65) $[M+H]^+$, 329 (50) $[M-H]^+$, 275 (35) $[M - t\text{Bu}+H]^+$, 273 (55) $[M - t\text{Bu} - H]^+$, 91 (100); HRMS (FAB, 3-NBA): calcd for $C_{19}H_{27}N_2O_3$: 331.2022, found: 331.2035.

3-(*tert*-Butyloxycarbonyl)-7-benzyl-9-(4′-carboxybutylidene)-3,7-diazabicyclo[3.3.1]-nonane (19): Potassium-*tert*-butoxide (1.36 g, 12.1 mmol) was added in portions at 0 °C to a suspension of (4-carboxybutyl)-triphenylphosphonium bromide (2.68 g, 6.05 mmol) in THF (60 mL). The suspension was warmed to room temperature and stirred for 30 min. After cooling to − 20 °C a solution of bispidinone **18** (500 mg, 1.51 mmol) in THF (10 mL) was added slowly. The mixture was warmed to room temperature slowly and stirred for 2.5 h. The suspension was poured on sat. NH_4Cl solution (150 mL) and extracted with chloroform (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (chloroform/methanol 20:1) to yield an oil (424 mg, 1.02 mmol, 68 %). $R_f =$ 0.23 (chloroform/methanol 20:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.35 –$ 7.21 (m, 5H; arom. H), 5.24 (t, $J = 8$ Hz, 1H; CH=), 4.29 – 4.19 (m, 1H; cycl. NCH_2), 4.12 – 4.02 (m, 1H; cycl. NCH_2), 3.53 – 3.38 (m, 2H; NCH_2Ph), 3.10 – 2.90 (m, 4H; cycl. NCH_2), 2.74 – 2.67 (m, 1H; $CHCH_2N$), 2.40 – 2.22 (m, 3H; $CHCH_2N$ and cycl. NCH_2), 2.33 (t, $J = 9$ Hz, 2H; CH_2COOH), 2.09 – 2.03 (m, 2H; $CH_2CH{=}$), 1.70 (dt, $J = 7$ Hz, 2H; CH_2CH_2COOH), 1.50 (s, 9H; $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 178.8$ (COOH), 155.3 (C=O urethane), 139.8 (*C*=CH), 138.0 (arom. C), 129.1, 128.4, 127.2 (arom. CH), 119.8 (*C*H=C), 79.5 ($C(CH_3)_3$), 62.7 (CH_2Ph), 60.0, 59.3 ($CH_2N(7)$), 51.0, 50.2, 49.4 ($CH_2N(3)$), 40.81 (*C*HC=), 34.0 (CH_2COOH), 33.5 (*C*HC=), 22.9 ($(CH_3)_3C$), 26.3 ($CH_2CH{=}$), 25.3 (CH_2CH_2COOH); IR (KBr): $\tilde{\nu} =$ 2797 (Bohlmann-band),[29] 1693 cm^{-1} (C=O); MS (FAB, glycerol): *m*/*z* (%): 415 (85) $[M+H]^+$, 413 (15) $[M-H]^+$, 359 (40) $[M - t\text{Bu}+H]^+$, 357 (20) $[M - t\text{Bu} - H]^+$, 315 (10) $[M - \text{Boc}+H]^+$, 91 (70); HRMS (FAB, glycerol): calcd for $C_{24}H_{35}N_2O_4$: 415.2600, found: 415.2624.

3-(*tert*-Butyloxycarbonyl)-9-(4′-carboxybutyl)-7-(9″-fluorenylmethyloxycarbonyl)-3,7-diazabicyclo[3.3.1]nonane (20): PD/C (10 %, 150 mg) was added to a solution of bispidine derivative **19** (338 mg, 0.815 mmol) in ethanol (7 mL). The atmosphere was exchanged for hydrogen three times. The suspension was stirred overnight, filtered over Celite and evaporated in vacuo. The residual oil was taken up in a suspension of 1N $NaHCO_3$ (5 mL) and THF (2.5 mL) and cooled to 0 °C. To this suspension was added dropwise a solution of Fmoc-Cl (316 mg, 1.22 mmol) in THF (2.5 mL). After warming to room temperature the suspension was stirred overnight. The pH was lowered to 3 with 1N HCl and the solution was extracted with chloroform (3 × 40 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate 3:1, 1 % acetic acid) to yield an oil (309 mg, 0.563 mmol, 69 %). $R_f = 0.32$ (cyclohexane/ethyl acetate 3:1, 1 % acetic acid); ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of diastereomers): $\delta = 7.75$ (d, $J = 7$ Hz, 2H; Fmoc-CH), 7.63 (d, $J = 7$ Hz, 1H; Fmoc-CH), 7.56 (d, $J = 7$ Hz, 1H; Fmoc-CH), 7.38 (t, $J =$ 7 Hz, 2H; Fmoc-CH), 7.31 (t, $J = 7$ Hz, 2H; Fmoc-CH), 4.34 – 3.90 (m, 7H; Fmoc-CH_2, Fmoc-CH, cycl. NCH_{2eq}), 3.28 – 2.95 (m, 4H; cycl. NCH_{2ax}), 2.36 (t, $J = 7$ Hz, 2H; CH_2COOH), 1.74 – 1.62 (m, 5H; $CHCH$ (3H), CH_2CH_2COOH), 1.57 – 1.31 (m, 4H; $CH_2(CH_2)_2COOH$, $CH_2(CH_2)_3COOH$), 1.45 (s, 9H; $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 100.6 MHz, mixture of diastereomers): $\delta = 178.6$ (COOH), 155.8, 155.3, 155.0 (C=O urethane), 144.8, 144.2, 141.6, 141.4 (quart., Fmoc), 127.8, 127.7, 127.3, 125.6, 125.3, 120.1 (Fmoc-CH), 79.9 ($C(CH_3)_3$), 67.7 (Fmoc-CH_2), 50.9, 50.8 (CH_2NBoc), 47.5 (Fmoc-CH), 43.3, 42.3 (CH_2NFmoc), 38.3 ($CHCH_2N$), 34.1 (CH_2COOH), 31.8 ($CH_2(CH_2)_4COOH$), 30.3 ($CH_2(CH_2)_3COOH$), 28.6 ($(CH_3)_3C$), 26.5 ($CH_2(CH_2)_2COOH$), 25.0 (CH_2CH_2COOH); IR (KBr): $\tilde{\nu} = 2866$ (Bohlmann-band),[29] 1708 cm^{-1} (C=O); MS (FAB, glycerol): *m*/*z* (%): 547 (3) $[M-H]^+$, 493 (10) $[M - t\text{Bu}+H]^+$; HRMS (FAB, glycerol): calcd for $C_{32}H_{41}N_2O_4$: 549.2965, found: 549.2978.

Coupling of ligand precursors to the solid phase

a) Boc-oxa-bispidine system 9: A solution of Boc-oxa-bispidine acid **7** (210 mg, 0.645 mmol), *N*,*N*′-diisopropylcarbodiimde (133 μL, 0.859 mmol) and DMAP (10 mg, 0.082 mmol) in CH_2Cl_2 (8 mL) was added to hydroxymethylpolystyrene (495 mg, 0.87 mmol g^{-1}, 0.431 mmol) in a syringe reactor. The reactor was shaken overnight, and the resin was washed with CH_2Cl_2 (3 ×) and dried in vacuo. The yield of the anchoring reaction was determined from the total mass of the resin after the procedure (for different loadings of the resin, the amount of Boc-oxa-bispidine acid **7** was increased or lowered accordingly). Yield: 590 mg (71 %, equals 0.52 mmol g^{-1}).

b) Boc-Fmoc-bispidine system 21: A solution of Boc-Fmoc-bispidine acid **20** (395 mg, 0.720 mmol), *N*,*N*′-diisopropylcarbodiimde (143 μL, 0.919 mmol) and DMAP (10 mg, 0.082 mmol) in CH_2Cl_2 (8 mL) was added to hydroxymethylpolystyrene (480 mg, 0.87 mmol g^{-1}, 0.418 mmol) in a syringe reactor. The reactor was shaken overnight and the resin was washed with DMF (2 ×) and CH_2Cl_2 (3 ×) and dried in vacuo. Yield: 690 mg (94 %, equals 0.61 mmol g^{-1}).

Loading according to UV absorption of fulvene/piperidine adduct after cleavage of the Fmoc group: 0.58 mmol g^{-1}.

c) Capping: Capping was performed twice for 10 min with each a mixture of acetic anhydride, pyridine and CH_2Cl_2 (1:2:2). The resin was washed with CH_2Cl_2 (5 ×) and dried in vacuo.

0947-6539/02/0820-4776 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 20

Synthesis of phosphoramidite ligands on solid support: The following general procedures were used as required for the synthesis of the individual ligand system on solid support.

a) Cleavage of the Fmoc protecting group: A mixture of DMF and piperidine (4:1, 2 mL) was added to Boc-Fmoc-bispidine resin **21** (55 mg, 0.032 mmol) in a syringe reactor, and the mixture was shaken for 15 min. The resin was washed with CH_2Cl_2 (3 ×) and dried in vacuo.

b) Acylation: To the resin after Fmoc-cleavage (0.032 mmol) in a syringe reactor, was added either [i) acid anhydride (0.16 mmol) and DMAP (2 mg, 0.016 mmol) in pyridine/CH_2Cl_2 (1.5 mL, 1:1) or ii) acid chloride (0.16 mmol) and DMAP (2 mg, 0.016 mmol) in pyridine/CH_2Cl_2 (2 mL, 1:1) or iii) acid (0.16 mmol, activated with HATU (55 mg, 0.14 mmol) and iPr$_2$EtN (60 μL, 0.35 mmol) in CH_2Cl_2 (1.5 mL) for 30 min] and shaken overnight. The resin was washed with DMF (2 ×) and CH_2Cl_2 (4 ×).

c) Urea and thiourea groups: To the resin after Fmoc cleavage (0.032 mmol) in a syringe reactor, was added a solution of phenyl isocyanate (0.16 mmol, 19 mg) and phenyl isothiocyanate (0.16 mmol, 21.6 mg) in CH_2Cl_2 (2 mL). The reaction mixture was shaken for overnight and washed with DMF (3 ×) and CH_2Cl_2 (5 ×).

d) Reductive amination: To the resin after Fmoc cleavage (0.032 mmol) in a syringe reactor, was added the aldehyde (10 equiv, 0.32 mmol) and $NaCNBH_3$ (0.64 mmol, 40 mg) in a mixture of methanol/CH_2Cl_2 (2 mL, 1.5:1). The mixture was shaken overnight and washed with methanol (2 ×), methanol/CH_2Cl_2 (1:1) and CH_2Cl_2 (4 ×).

e) Tosylation, phosphorylation: To the resin after Fmoc cleavage (0.032 mmol) in a syringe reactor, was added either [i) a solution of toluene-4-sulfonyl chloride (0.16 mmol, 30.5 mg), ii) a solution of chlorodiphenylphosphine (0.16 mmol, 30 μL) or iii) a solution of phosphoric acid diphenylester chloride (0.16 mmol, 33 μL)] and triethylamine (0.22 mmol, 31 μL) in CH_2Cl_2 (1.5 mL) (for chlorodiphenylphosphine: toluene instead of CH_2Cl_2). The mixture was shaken overnight and washed with DMF (2 ×) and CH_2Cl_2 (4 ×).

f) Amino acids: After Fmoc cleavage to the resin (0.032 mmol) in a syringe reactor, was added a solution of Fmoc-amino acid (0.16 mmol), HBTU (0.16 mmol, 60.6 mg), HOBT (0.16 mmol, 21.6 mg) and DIPEA (0.16 mmol, 20 mg) in CH_2Cl_2/DMF (2 mL, 1:1) and the mixture was shaken for 3 h. The resin was washed with DMF (3 ×) and CH_2Cl_2 (5 ×) and dried in vacuo.

The yield was quantitative, as determined by Fmoc-cleavage. The Fmoc group was again deprotected and the amino acid was treated with i) Ac_2O (0.16 mmol, 16.3 mg) and DMAP (0.016 mmol, 2 mg) in pyridine/CH_2Cl_2 (2 mL, 1:1), ii) methanesulfonyl chloride (0.16 mmol, 18.2 mg), iii) benzenesulfonyl chloride (0.16 mmol, 28 mg) or iv) toluene-4-sulfonyl chloride (0.16 mmol, 30.5 mg) and DIPEA (0.32 mmol). The reaction mixture was shaken for overnight and washed with DMF (2 ×) and CH_2Cl_2 (4 ×).

g) Dipeptides: In a syringe reactor, the Fmoc group of the amino acid derivatives as described above was removed and treated again with another Fmoc-amino acid (0.16 mmol) as mentioned above. After subsequent Fmoc removal, the liberated amine was treated with Ac_2O, methanesulfonyl chloride or toluene-4-sulfonyl chloride (0.16 mmol) as described above. The resin was washed with DMF (3 ×) and CH_2Cl_2 (5 ×).

h) Cleavage of the Boc protecting group: To the resin from steps b)–g) (0.032 mmol) or the Boc-oxa-bispidine resin **9** (0.032 mmol) in a syringe reactor, was added a solution of trifluoroacetic acid (1 mL) in CH_2Cl_2 (1 mL). The mixture was shaken for 30 min and washed with CH_2Cl_2 (5 ×). A solution of triethylamine (0.5 mL) in CH_2Cl_2 (2 mL) was added and the mixture was shaken for 15 min, washed with CH_2Cl_2 (5 ×) and dried in vacuo to yield the free amine base.

i) Coupling to the phosphoramidite (bispidine and chlorophosphite): The corresponding solid BINOL-chlorophosphite **10a**, **10b**, **10c** or **10d** (0.16 mmol) was added under argon to the resin in a syringe reactor after Boc cleavage (0.032 mmol). Immediately a solution of triethylamine (0.32 mmol, 44 μL) in toluene (1.5 mL) was added and the mixture was shaken overnight. The mixture was washed with DMF (2 ×) and CH_2Cl_2 (4 ×) and dried in vacuo.

j) Coupling to the phosphoramidite (bispidine and PCl_3/BINOL): A solution of PCl_3 (28 μL, 0.32 mmol) in THF (1 mL) and a solution of triethylamine (44 μL, 0.32 mmol) in THF (1 mL) was added to the resin (0.032 mmol) in a syringe reactor after Boc cleavage. The mixture was shaken for 1 h and washed with THF (2 ×). To the resin was added a solution of (*R*)-2,2′-dihydroxy-[1,1′]-binaphthyl (46 mg, 0.16 mmol) and triethylamine (44 μL, 0.32 mmol) in THF (2 mL). The mixture was shaken overnight and washed with DMF (2 ×) and CH_2Cl_2 (4 ×) and dried in vacuo.

Conjugate addition with polymer-bound ligands: **3-Ethylcyclohexanone**: A solution of copper(II)-trifluoromethanesulfonate (63 mg, 0.175 mmol) in CH_2Cl_2 (3 mL) and DMF (0.1 mL) was added to the phosphoramidite resin (0.032 mmol) in a syringe reactor. The mixture was shaken for 1 h and washed with a mixture of CH_2Cl_2/DMF (3:0.1, 1 ×) and CH_2Cl_2 (5 ×). After drying in vacuo a light brown to deep green resin was obtained.

To this resin (0.032 mmol) in a round-bottomed flask under argon was added a mixture of toluene (2.4 mL) and CH_2Cl_2 (0.4 mL) and the mixture was stirred slowly for 15 min at 0 °C.

To this mixture was added cyclohexen-2-one (77 μL, 0.80 mmol) and diethylzinc (0.96 mL, 1M solution in toluene, 0.96 mmol). The yellow, heterogeneous reaction mixture was stirred for 2 h at 0 °C. Then 1N HCl (5 mL) was added and the mixture was stirred for 30 min thoroughly. The mixture was transferred to a separation funnel and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and examined by gas chromatography.

Below all results obtained with different ligands are presented in tabulated form. The coding of the different ligands is explained in Figure 1–4 (see Results and Discussion). Analytical data of the products are given above (Table 3).

Table 3. Analytical data for the different products.

Compound	Conversion [%]	*ee* [%]	Compound	Conversion [%]	*ee* [%]
A1-B1-C1	94	11	**A1-B24-C1**	84	33
A1-B2-C1	quant.	39	**A1-B25-C1**	quant.	36
A1-B3-C1	quant.	44	**A1-B26-C1**	quant.	50
A1-B4-C1	quant.	29	**A1-B27-C1**	quant.	38
A1-B5-C1	quant.	21	**A1-B28-C1**	quant.	41
A1-B6-C1	83	35	**A2-C1**	quant.	39
A1-B7-C1	81	27	**A2-C2**	quant.	45
A1-B8-C1	quant.	23	**A2-C3**	quant.	39
A1-B9-C1	74	21	**A2-C4**	quant.	36
A1-B10-C1	quant.	18	**A3-C1**	77	18
A1-B11-C1	98	11	**A4-C1**	quant.	36
A1-B12-C1	quant.	32	**A4-C2**	94	32
A1-B13-C1	quant.	38	**A4-C3**	quant.	30
A1-B14-C1	quant.	31	**A5-C1**	97	29
A1-B15-C1	98	35	**A1-B3-C2**	quant.	67
A1-B16-C1	97	21	**A1-B3-C3**	82	21
A1-B17-C1	quant.	12	**A1-B3-C4**	quant.	38
A1-B18-C1	quant.	19	**A1-B13-C2**	quant.	54
A1-B19-C1	80	29	**A1-B13-C3**	quant.	49
A1-B20-C1	quant.	56	**A1-B13-C4**	quant.	38
A1-B21-C1	quant.	51	**A1-B20-C2**	quant.	46
A1-B22-C1	78	19	**A1-B26-C2**	98	41
A1-B23-C1	73	27			
C1-AA1-D1	41	7	**C1-AA5-D3**	65	3
C1-AA2-D1	75	11	**C1-AA6-D3**	61	20
C1-AA3-D1	64	10	**C1-AA1-D4**	76	30
C1-AA4-D1	80	7	**C1-AA2-D4**	63	24
C1-AA5-D1	69	6	**C1-AA3-D4**	90	34
C1-AA1-D2	56	5	**C1-AA4-D4**	78	23
C1-AA2-D2	66	13	**C1-AA5-D4**	65	12
C1-AA3-D2	69	15	**C1-AA7-D4**	80	29
C1-AA4-D2	34	9	**C1-AA1-AA3-D1**	71	12
C1-AA5-D2	56	3	**C1-AA2-AA3-D1**	48	7
C1-AA6-D2	69	13	**C1-AA1-AA3-D2**	72	15
C1-AA1-D3	68	31	**C1-AA2-AA3-D2**	84	14
C1-AA2-D3	70	25	**C1-AA1-AA3-D4**	83	19
C1-AA3-D3	78	23	**C1-AA2-AA3-D4**	83	21
C1-AA4-D3	52	21			

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3-(*tert*-Butyloxycarbonyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane (26): Toluene-4-sulfonylhydrazide (584 mg, 3.14 mmol) and toluene-4-sulfonic acid (64 mg, 0.34 mmol) was added to a suspension of bispidinone **18** (740 mg, 2.24 mmol) in DMF (12 mL). The mixture was heated to 100 °C for 10 min. Then sodium cyanoborohydride (704 mg, 11.2 mmol) was added and the mixture was further heated for 2 h to 100 °C. After cooling, toluene (100 mL) was added and the mixture was washed with water (50 mL), 1N $NaHCO_3$ solution (50 mL) and water (50 mL) and then dried over $MgSO_4$. The organic solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 4:1) to yield a colourless oil (302 mg 0.95 mmol, 43 %). $R_f = 0.42$ (cyclohexane/ethyl acetate 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.34 - 7.18$ (m, 5H; arom. H), 4.16 (d, $J = 13$ Hz, 1H; CH_{2eq}N(3), 3.99 (d, $J = 13$ Hz, 1H; CH_{2eq}N(3), 3.43 (d, $J = 14$ Hz, 1H; CH_2Ph), 3.30 (d, $J = 14$ Hz, 1H; CH_2Ph), 3.09 (d, $J = 13$ Hz, 1H; CH_{2eq}N(3), 3.04 (d, $J = 13$ Hz, 1H; CH_{2eq}N(3), 2.98 (d, $J = 11$ Hz, 1H; CH_{2eq}N(7), 2.88 (d, $J = 11$ Hz, 1H; CH_{2eq}N(7), 2.21 (d, $J = 11$ Hz, 1H; CH_{2ax}N(7), 2.16 (d, $J = 11$ Hz, 1H; CH_{2ax}N(7), 1.86 (brs, 1H; C*H*CH_2O), 1.78 (brs, 1H; C*H*CH_2O), 1.68 – 1.58 (m, 2H; CH_2-bridge), 1.59 (s, 9H; $(CH_3)_3$C); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 155.3$ (C=O), 139.2 (arom. C), 128.8, 128.3, 126.8 (arom. CH), 78.9 ($C(CH_3)_3$), 63.7 (CH_2Ph), 59.2, 59.0 (CH_2N(7)), 48.6, 47.8 (CH_2N(3)), 31.4 (CH_2-bridge), 29.2 (*C*HCH_2N), 28.9 (($CH_3)_3$C); IR (KBr): $\tilde{\nu} = 2795$ (Bohlmann-band[29]), 1692 cm^{-1} (C=O); MS (FAB, 3-NBA): *m*/*z* (%): 317 (45) $[M+H]^+$, 316 (60) $[M]^+$, 315 (35) $[M-H]^+$, 261 (45) $[M - t\text{Bu}+H]^+$, 260 (40) $[M - t\text{Bu}]^+$, 259 (100) $[M - t\text{Bu} - H]^+$, 215 (15) $[M - \text{Boc}+H]^+$; HRMS (FAB, 3-NBA): calcd for $C_{19}H_{28}N_2O_2$: 316.2151, found: 316.2169.

3-(*tert*-Butyloxycarbonyl)-7-(2′,2′-dimethylpropionyl)-3,7-diazabicyclo[3.3.1]nonane (28): Pd/C (250 mg, 10 %) was added to a suspension of bispidine **26** (241 mg, 0.76 mmol) in ethanol (5 mL). The atmosphere was exchanged for hydrogen three times. The mixture was stirred overnight and the progress of the reaction was checked by TLC. If some starting material was still remaining further palladium on charcoal (250 mg) was added and proceeded as above. The mixture was filtered over Celite and the solvent was evaporated in vacuo. The residue was taken up in pyridine (7 mL) and treated with DMAP (10 mg, 0.08 mmol) and pivaloyl anhydride (1.55 mL, 7.62 mmol). The mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo and the residue was taken up in CH_2Cl_2 (30 mL). This mixture was washed once with 1N HCl (15 mL), 1N $NaHCO_3$ (15 mL) and saturated NaCl solution (15 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 2:1) to yield an colourless oil (169 mg, 0.54 mmol, 71 %). $R_f = 0.33$ (cyclohexane/ethyl acetate 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 4.54$ (d, $J = 13$ Hz, 1H; CH_{2eq}N(3), 4.34 (d, $J = 13$ Hz, 1H; CH_{2eq}N(3), 4.20 (d, $J = 12$ Hz, 1H; CH_{2eq}N(7), 4.07 (d, $J = 12$ Hz, 1H; CH_{2eq}N(7), 3.21 – 2.96 (m, 4H; CH_2N), 1.94 (brs, 2H; *CH*CH_2N), 1.83 – 1.74 (m, 2H; CH_2-bridge), 1.42 (s, 9H; $(CH_3)_3$C, Boc), 1.27 (s, 9H; $(CH_3)_3$C, Piv); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 177.1$ (C=O, Piv), 154.9 (C=O, Boc), 79.6 ($C(CH_3)_3$, Boc), 50.6, 48.8, 47.4 (CH_2N), 39.1 ($C(CH_3)_3$, Piv), 31.3 (CH_2-bridge), 28.9 (($CH_3)_3$C, Boc), 28.6 (($CH_3)_3$C, Piv), 28.4, 28.2 (*C*HCH_2N); IR (KBr): $\tilde{\nu} = 2843$ (Bohlmann-band[29]), 1676, 1626 cm^{-1} (C=O); MS (FAB, 3-NBA): *m*/*z* (%): 333 (7) $[M+Na]^+$, 311 (10) $[M+H]^+$, 255 (100) $[M - t\text{Bu}+H]^+$, 209 (40) $[M - \text{Boc}]^+$; HRMS (FAB, 3-NBA): calcd for $C_{17}H_{31}N_2O_3$: 311.2335, found: 311.2337.

7-(*tert*-Butyloxycarbonyl)-3-(toluene-*p*-sulfonyl)-diazabicyclo[3.3.1]nonane (29): The procedure for the synthesis of pivaloyl-bispidine **28** for the cleavage of the benzyl group by catalytic hydrogenation was followed. The residue was taken up in pyridine (7 mL) and treated with DMAP (10 mg, 0.08 mmol) and toluene-4-sulfonylchloride (726 mg, 3.81 mmol). The mixture was stirred overnight and the solvent was evaporated in vacuo. The residue was taken up in CH_2Cl_2 (30 mL) and was washed with 1N HCl (15 mL), 1N $NaHCO_3$ (15 mL) and sat. NaCl solution (15 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 2:1) to yield a colourless solid (210 mg, 0.55 mmol, 72 %). $R_f = 0.32$ (cyclohexane/ethyl acetate 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.60$ (d, $J = 8$ Hz, 2H; arom. Tos), 7.31 (d, $J = 8$ Hz, 2H; arom. Tos), 4.30 (d, $J = 13$ Hz, 1H; CH_{2eq}N(7), 4.16 (d, $J = 13$ Hz, 1H; CH_{2eq}N(7), 3.81 (d, $J = 11$ Hz, 1H; CH_{2eq}N(3), 3.74 (d, $J = 11$ Hz, 1H; CH_{2eq}N(3), 3.12 (d, $J = 13$ Hz, 1H; CH_{2ax}N(7), 3.01 (d, $J = 13$ Hz, 1H; CH_{2ax}N(7), 2.55 (d, $J = 11$ Hz, 1H; CH_{2ax}N(3), 2.51 (d, $J = 11$ Hz, 1H; CH_{2ax}N(3), 2.42 (s, 3H; CH_3 Tos), 1.91 (brs, 2H; *CH*CH_2N), 1.70 (m, 1H; CH_2-bridge), 1.52 (s, 9H; $(CH_3)_3$C), 1.46 (m, 1H; CH_2-bridge); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 155.5$ (C=O), 143.4, 132.6 (arom. C), 129.6, 128.0 (arom. CH), 79.8 ($C(CH_3)_3$), 50.5, 50.4 0 (CH_2N(3)), 48.2, 47.3 (CH_2N(7)), 30.3 (CH_2-bridge), 28.7 (($CH_3)_3$C), 27.9 (*C*HCH_2N), 21.7 (CH_3 Tos); IR (drift): $\tilde{\nu} = 2838$ (Bohlmann-band[29]), 1698 cm^{-1} (C=O); MS (FAB, 3-NBA): *m*/*z* (%): 403 (5) $[M+Na]^+$, 381 (5) $[M+H]^+$; HRMS (EI, 70 eV): calcd for $C_{19}H_{29}N_2O_4S$: 381.1849, found: 381.1846.

7-(*tert*-Butyloxycarbonyl)-3-oxa-7-azabicyclo[3.3.1]nonane (30): Toluene-4-sulfonylhydrazide (259 mg, 1.39 mmol) and toluene-4-sulfonic acid (28 mg, 0.23 mmol) were added to a solution of bispidinone **6** (240 mg, 0.99 mmol) in DMF (5 mL) and the mixture was heated for 10 min to 100 °C. Then sodium cyanoborohydride (313 mg, 4.97 mmol) was added and the mixture was further heated for 2 h to 100 °C. After cooling toluene (30 mL) was added and the mixture was washed with water (15 mL), 1N $NaHCO_3$ solution (15 mL) and water (15 mL) and dried over $MgSO_4$. The organic solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 4:1) to yield a colourless solid (108 mg, 0.47 mmol, 48 %). M.p. 39 °C; $R_f = 0.34$ (cyclohexane/ethyl acetate 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 4.34$ (d, $J = 13$ Hz, 1H; CH_{2eq}N), 4.19 (d, $J = 13$ Hz, 1H; CH_{2eq}N), 4.01 (d, $J = 11$ Hz, 1H; CH_{2eq}O), 3.95 (d, $J = 11$ Hz, 1H; CH_{2eq}O), 3.73 (d, $J = 11$ Hz, 1H; CH_{2ax}O), 3.70 (d, $J = 11$ Hz, 1H; CH_{2ax}O), 3.14 (d, $J = 13$ Hz, 1H; CH_{2ax}N), 3.04 (d, $J = 13$ Hz, 1H; CH_{2ax}N), 1.95 – 1.91 (m, 1H; C*H*CH_2O), 1.82 – 1.78 (m, 1H; C*H*CH_2O), 1.67 (brs, 1H; CH_2-bridge), 1.47 (brs, 1H; CH_2-bridge), 1.47 (s, 9H; $(CH_3)_3$C); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 155.5$ (C=O urethane), 79.3 ($C(CH_3)_3$), 72.3, 72.2 (CH_2O), 49.0, 48.0 (CH_2N), 31.2 (CH_2-bridge), 29.7, 29.6 (*C*HCH_2O), 28.7 (($CH_3)_3$C); IR (drift): $\tilde{\nu} = 2863$ (Bohlmann-band[29]), 1709 cm^{-1} (C=O); MS (EI, 70 eV): *m*/*z* (%): 227 (30) $[M]^+$, 171 (50) $[M - t\text{Bu}]^+$, 127 (35) $[M - \text{Boc}]^+$; HRMS (EI, 70 eV): calcd for $C_{12}H_{21}NO_3$: 227.1521, found: 227.1523.

3-(Toluene-*p*-sulfonyl)-3,7-diazabicyclo[3.3.1]nonane-7-[(*R*)-binaphthyl-2,2′-diyl]-phosphite (31): Trifluoroacetic acid (0.5 mL) was added to a suspension of Boc-bispidine **29** (70 mg, 0.26 mmol) in CH_2Cl_2 (0.5 mL) and the solution was stirred at room temperature for 30 min. After evaporation of the solvent in vacuo and coevaporation with toluene the residue was taken up in toluene (2 mL) and treated with triethylamine (262 μL, 1.89 mmol). To this mixture was added slowly a solution of chlorophosphite **10** (86 mg, 0.245 mmol) in toluene (3 mL) and the mixture was heated for 5 h at 80 °C. The precipitate was filtered off and the solvent was evaporated in vacuo. The residue was purified by flash chromatography over Florisil (treated with triethylamine) with cyclohexane/CH_2Cl_2 2:1, 2 % triethylamine to yield a colourless solid (50 mg, 0.094 mmol, 51 %). $R_f = 0.95$ (CH_2Cl_2/Et_3N 10:1); m.p. 230 – 231 °C; $[\alpha]_D^{20} = -297$ ($c = 0.85$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.97 - 7.86$ (m, 4H; arom., BINOL), 7.76 (d, $J = 9$ Hz, 1H; arom., BINOL), 7.62 (d, $J = 8$ Hz, 2H; arom., Tos), 7.45 – 7.20 (m, 9H; arom., BINOL, Tos), 3.74 – 3.63 (m, 3H; CH_2N), 3.37 – 3.27 (m, 2H; CH_2N), 2.61 – 2.48 (m, 3H; CH_2N), 2.43 (s, 3H; CH_3), 1.85 (brs, 1H; *CH*CH_2N), 1.68 – 1.59 (m, 2H; CH_2-bridge), 1.51 (brs, 1H; *CH*CH_2N); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 150.2$, 150.1 (arom. C, BINOL), 143.2, 132.8 (arom. C, Tos), 132.9, 131.6, 130.9, 123.9, 123.6 (arom. C, BINOL), 130.5, 130.0, 128.6, 128.4, 127.4, 127.1, 126.1, 126.0, 124.7, 124.6 (arom. CH, BINOL), 129.7, 128.0 (arom. CH, Tos), 50.4, 50.0, 49.4, 46.6 (CH_2N), 30.7 (CH_2-bridge), 27.8, 27.1 (*C*HCH_2N), 21.7 (CH_3); ^{31}P NMR ($CDCl_3$, 202.5 MHz): $\delta = 147.8$; IR (drift): $\tilde{\nu} = 2848$ (Bohlmann-band[29]), 1698 cm^{-1} (C=O); MS (FAB, 3-NBA): *m*/*z* (%): 595 (20) $[M+H]^+$, 439 (15) $[M - \text{Tos} - H]^+$; HRMS (FAB, 3-NBA): calcd for $C_{34}H_{32}N_2O_4PS$: 595.1821, found: 595.1835.

7-(2′,2′-Dimethylpropionyl)-3,7-diazabicyclo[3.3.1]nonane-3-[(*R*)-(3,3′-dimethyl)-binaphthyl-2,2′-diyl]phosphite (32): Trifluoroacetic acid (0.5 mL) was added to a suspension of Boc-bispidine **28** (50.6 mg, 0.163 mmol) in CH_2Cl_2 (0.5 mL) and the reaction was stirred at room temperature for 30 min. After evaporation of the solvent in vacuo and coevaporation with toluene the residue was taken up in 2N KOH solution (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The crude product was taken up in THF (1.5 mL) and this solution was added slowly to a mixture of PCl_3 (20 μL, 0.228 mmol) and triethylamine (33 μL, 0.238 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 45 min at 0 °C. To this mixture was added dropwise a solution of (*R*)-(3,3′-dimethyl)binaphthyl-

0947-6539/02/0820-4778 $ 20.00+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 20

2,2′-diol **35** (118 mg, 0.375 mmol) and triethylamine (66 μL, 0.476 mmol) in THF (2 mL) at 0 °C. After warming to room temperature the mixture was stirred for 1.5 h, filtered and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on Florisil (treated with triethylamine) with cyclohexane/CH_2Cl_2 2:1, 2% triethylamine to yield a colourless solid (27 mg, 0.049 mmol, 30%). $R_f = 0.95$ (CH_2Cl_2/Et_3N 10:1); m.p. 153 °C; $[\alpha]_D^{20} = -299$ ($c = 0.69$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.82-7.73$ (m, 4H; arom. H), 7.38–7.10 (m, 6H; arom. H), 3.98–3.93 (m, 2H; CH_2N), 3.66–3.61 (m, 2H; CH_2N), 3.26–3.21 (m, 3H; CH_2N), 2.58 (s, 3H; CH_3, BINOL), 2.51 (s, 3H; CH_3, BINOL), 2.20 (d, $J = 12$ Hz, 1H; CH_2N), 1.97 (br s, 1H; $CHCH_2N$), 1.65–1.59 (m, 3H; CH_2-bridge, $CHCH_2N$), 1.32 (s, 9H; $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 176.5$ (C=O), 149.1, 148.6, 131.6, 131.5, 131.2, 129.5 (arom. C), 129.6, 129.4, 127.5, 127.4, 127.0, 126.8, 125.1, 125.0, 124.7, 124.5 (arom. CH), 50.0, 49.5, 47.1, 46.3 (CH_2N), 38.9 ($C(CH_3)_3$), 28.6 ($(CH_3)_3C$), 28.2, 28.0 ($CHCH_2N$), 26.9 (CH_2-bridge), 18.0, 17.6 (CH_3 BINOL); ^{31}P NMR ($CDCl_3$, 202.5 MHz): $\delta = 145.5$; IR (drift): $\tilde{\nu} = 2850$ (Bohlmann-band[29]), 1629 cm^{-1} (C=O); MS (FAB, 3-NBA): m/z (%): 553 (90) $[M+H]^+$, 343 (80) $[Me_2BINOLP]^+$, 209 (65) $[M - Me_2BINOLP]^+$; HRMS (FAB, 3-NBA): calcd for $C_{34}H_{18}N_2O_3P$: 553.2620, found: 553.2601.

3-(Toluene-*p*-sulfonyl)-3,7-diazabicyclo[3.3.1]nonane-7-[(*R*)-(3,3′-dimethyl)binaphthyl-2,2′-diyl]phosphite (33): Trifluoroacetic acid (0.5 mL) was added to a suspension of Boc-bispidine **29** (60 mg, 0.158 mmol) in CH_2Cl_2 (0.5 mL) and the mixture was stirred for 30 min. After evaporation of the solvent in vacuo and coevaporation with toluene the residue was taken up in 2N KOH solution (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The crude product was taken up in THF (1.0 mL) and was slowly added to a mixture of PCl_3 (17 μL, 0.197 mmol) and triethylamine (29 μL, 0.208 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 45 min at 0 °C. To this mixture was added dropwise a solution of (*R*)-(3,3′-dimethyl)binaphthyl-2,2′-diol (93 mg, 0.297 mmol) and triethylamine (45 μL, 0.326 mmol) in THF (1 mL) at 0 °C. After warming to room temperature the mixture was stirred for 1.5 h, filtered and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on Florisil (treated with triethylamine) with cyclohexane/CH_2Cl_2 2:1, 2% triethylamine to yield a colourless solid (11.8 mg, 0.019 mmol, 12%). $R_f = 0.95$ (CH_2Cl_2/Et_3N 10:1); m.p. 261–263 °C; $[\alpha]_D^{20} = -377$ ($c = 0.37$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.82-7.74$ (m, 4H; arom. H, BINOL), 7.58 (d, $J = 8$ Hz, 2H; arom. H, Tos), 7.38–7.11 (m, 8H; arom. H, BINOL, Tos), 3.65 (d, $J = 11$ Hz, 1H; $CH_{2eq}N(3)$, 3.56 (d, $J = 11$ Hz, 1H; $CH_{2eq}N(3)$, 3.35 (d, $J = 13$ Hz, 1H; $CH_{2eq}N(7)$, 3.24 (d, $J = 13$ Hz, 1H; $CH_{2eq}N(7)$, 2.68 (s, 3H; CH_3, BINOL), 2.64–2.23 (m, 4H; CH_2N), 2.50 (s, 3H; CH_3, BINOL) and 2.42 (s, 3H; CH_3, Tos), 1.91 (br s, 1H; $CHCH_2N$), 1.65–1.55 (m, 3H; CH_2-bridge, $CHCH_2N$); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 149.4$, 149.1 (arom. C, BINOL), 143.2, 132.7 (arom. C, Tos), 131.7, 131.5, 130.9 (arom. C, BINOL), 129.9 (arom. CH, BINOL), 129.7, 128.0 (arom. CH, Tos), 127.7, 127.6, 127.3, 126.9, 125.2, 125.0, 124.7, 124.6 (arom. CH, BINOL), 49.8, 49.5, 45.7 (CH_2N), 27.7 ($CHCH_2N$), 27.1 (CH_2-bridge), 27.0 ($CHCH_2N$), 21.7 (CH_3, Tos), 18.1, 17.8 (CH_3, BINOL); ^{31}P NMR ($CDCl_3$, 202.5 MHz): $\delta =$ 145.2; IR (drift): $\tilde{\nu} = 2833$ (Bohlmann-band[29]); MS (FAB, 3-NBA): m/z (%): 623 (15) $[M+H]^+$, 343 (10) $[Me_2BINOLP]^+$; HRMS (FAB, 3-NBA): m/z (%): calcd for $C_{36}H_{36}N_2O_4PS$: 623.2133, found: 623.2143.

3-Oxa-7-azabicyclo[3.3.1]nonane-7-[(*R*)-(3,3′-dimethyl)binaphthyl-2,2′-diyl]phosphite (34): Trifluoroacetic acid (1 mL) was added to a suspension of Boc-oxa-bispidine **30** (70 mg, 0.308 mmol) in CH_2Cl_2 (1 mL) and the mixture was stirred at room temperature for 30 min. After evaporation of the solvent in vacuo and coevaporation with toluene the residue was taken up in 2N KOH solution (5 mL) and extracted with diethyl ether (6 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The resulting waxy residue was taken up in THF (1.5 mL) and was added dropwise to a mixture of PCl_3 (27 μL 0.31 mmol) and triethylamin (45 μL, 0.32 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 45 min at 0 °C. To this mixture was added dropwise a solution of (*R*)-(3,3′-dimethyl)binaphthyl-2,2′-diol (106 mg, 0.34 mmol) and triethylamine (94 μL, 68 mg, 0.68 mmol) in THF (1.5 mL) at 0 °C. After warming to room temperature the mixture was stirred for 1.5 h, filtered and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on Florisil (treated with triethylamine) with cyclohexane/CH_2Cl_2 2:1, 2% triethylamine to yield a colourless solid (4 mg, 0.009 mmol, 3%). $R_f = 0.95$ (CH_2Cl_2/Et_3N 10:1); m.p. 167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.83$, 7.74 (m, 4H; arom. H), 7.39–7.33 (m, 3H; arom. H), 7.27–7.24 (m, 1H; arom. H), 7.21–7.13 (m, 2H; arom. H), 3.97 (d, $J = 11$ Hz, 1H; $CH_{2eq}O$), 3.88 (d, $J = 11$ Hz, 1H; $CH_{2eq}O$), 3.79 (d, $J = 11$ Hz, 1H; $CH_{2ax}O$), 3.73 (d, $J = 14$ Hz, 1H; CH_2N), 3.62 (d, $J =$ 11 Hz, 1H; $CH_{2ax}O$), 3.36 (d, $J = 13$ Hz, 1H; CH_2N), 3.32–3.28 (m, 1H; CH_2N), 2.60 (s, 3H; arom. CH_3), 2.50 (s, 3H; arom. CH_3), 2.46 (d, $J = 13$ Hz, CH_2N), 1.91–1.87 (m, 1H; $CHCH_2O$), 1.78–1.74 (m, 1H; $CHCH_2O$), 1.64 (s, 1H; CH_2-bridge), 1.56 (s, 1H; CH_2-bridge); ^{31}P NMR ($CDCl_3$, 202.5 MHz): $\delta = 145.8$; MS (FAB, 3-NBA): m/z (%): 470 (10) $[M+H]^+$, 469 (8) $[M]^+$, 343 (30) $[Me_2BINOLP]^+$; HRMS (FAB, 3-NBA): calcd for $C_{29}H_{29}NO_3P$: 470.1885, found: 470.1877.

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