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Combinatorial development of chiral phosphoramidite-ligands for enantioselective conjugate addition reactions

Oliver Huttenloch, Eltepu Laxman and Herbert Waldmann*

Max-Planck-Institut für molekulare Physiologie, Abteilung Chemische Biologie, Otto-Hahn-Str. 11, 44227 Dortmund, Germany, and Universität Dortmund, FB 3, Organische Chemie 44221 Dortmund, Germany. E-mail: herbert.waldmann@mpi-dortmund.mpg.de

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Chiral phosphoramidite ligands embodying bispidine frame work and a binaphthyl phosphoramidite for Cu-catalysed enantioselective conjugate addition reactions were developed employing principles of combinatorial and solid phase chemistry.

The application of combinatorial principles to the development of enantioselective catalysed transformations has opened up entirely new opportunities to the field. In particular, the approach to synthesize libraries of chiral ligands for metal atoms on polymeric supports and to apply them as heterogeneous catalysts in screening systems has emerged as a powerful technique for the rapid development of ultimately soluble ligands for enantioselective catalysis.[1,2] The successful use of this method requires that the polymer-bound catalysts display the same trends in stereoselection as the corresponding soluble catalyst systems.[2b,c,3]

For the enantioselective steering of conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds,[4] the use of dialkylzinc reagents in the presence of a Cu-catalyst and in the presence of chiral phosphoramidite ligands[4–6] is particularly efficient.

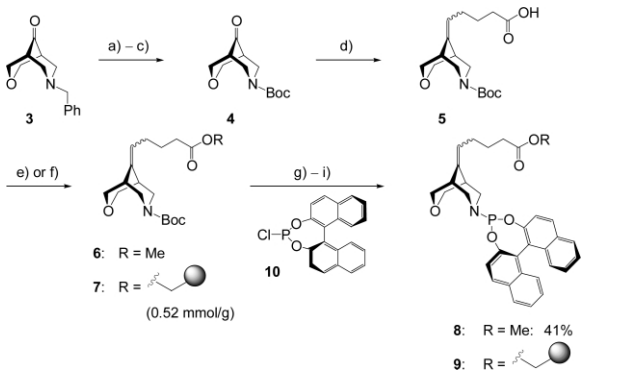
The application of the combinatorial principle of Cu-catalyzed enantioselective conjugate addition processes has been pursued only in a single case[7] in which solid-phase-extraction techniques were used for the generation of soluble sulfonamide ligands. However, the approach described above has not been applied to enantioselectively catalyzed conjugate addition reactions.

Here we describe the combinatorial synthesis of a library of polymer-bound bispidine-derived phosphoramidite ligands and its evaluation in the Cu-catalyzed enantioselective addition of dialkylzinc reagents to enones. We have recently shown that phosphoramidites embodying a binaphthol unit and a bispidine-derived modulating substituent, *e.g.* **1**, can successfully be employed for the steric steering of Cu-catalyzed enantioselective conjugate addition reactions.[8] In order to find more efficient catalysts embodying the same underlying structural motives it was decided to synthesize a library of ligands **2** (Fig. 1) on a polymeric support. To determine if the results to be expected from investigating such immobilized ligands would be comparable to the values recorded for soluble ligand **1** compounds **8** and **9** were synthesized as shown in Scheme 1.

Benzyl-protected bispidinone **3**[8,9] was converted into Boc-masked compound **4** which was subjected to a Wittig reaction yielding olefin **5**. The carboxylic acid moiety was then converted either to the methyl ester **6** or linked into hydroxymethyl polystyrene to give polymer **7** with a loading of 0.52 mmol g^{-1}. Removal of the Boc groups and phosphitylation with chlorophosphite **10**[10] yielded model compounds **8** and **9**.

Application of compounds **1**, **8** and **9** as ligands in the Cu-catalyzed addition of $ZnEt_2$ to cyclohexenone proceeded with comparable enantioselectivity (Scheme 2). Thus, at −30 °C ligands **1** and **8** yield addition product **12** with 43% ee and 46% ee, respectively, demonstrating that modification of the 9-position in the oxabispidine core does not negatively influence the efficiency of the stereoselection. Gratifyingly, immobilization of the ligand on polystyrene and performing the reaction at 0 °C instead of −30 °C (to ensure sufficient swelling) resulted in only a minor drop of the enantioselectivity to 39% ee. In order to reproducibly achieve this result, in the preparation of the catalyst, $Cu(OTf)_2$ had to be solubilized by addition of 3% DMF to the solvent CH_2Cl_2 before exposure to the immobilized phosphoramidite ligand.

For synthesizing a bispidine-phosphoramidite library bispidinone **14** was generated by double Mannich reaction from **13** and then converted into olefin **15** by means of a Wittig reaction. Exchange of the *N*-benzyl group for a Fmoc-urethane was accompanied by reduction of the double bond. The resulting Fmoc/Boc-protected bispidine carboxylic acid was linked to



Scheme 1 Synthesis of phosphoramidites **8** and **9**: (a) $ClCOOCH(Cl)CH_3$, CH_2Cl_2, Δ, 2 h; (b) MeOH, Δ, 2 h; (c) Boc_2O, KOH, H_2O, dioxane, rt, 12 h, 87% for three steps; (d) $Br^- Ph_3P^+(CH_2)_4COOH$, KO*t*Bu, THF, 0 °C→rt, 2.5 h, 54%; (e) EEDQ, MeOH, rt, 12 h, 82%; (f) hydroxymethylpolystyrene, DIC, DMAP, CH_2Cl_2, 12 h, rt, 71% (0.52 mmol g^{-1}), then Ac_2O, pyridine, CH_2Cl_2; (g) TFA, CH_2Cl_2, 0.5 h, rt, quant.; [(h) only on solid phase: Et_3N, CH_2Cl_2]; (i) chlorophosphite **10**, Et_3N, toluene, 12 h, 80 °C, 41% [for **7**: rt]; EEDQ = 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, DIC = *N*,*N*′-diisopropylcarbodiimide, DMAP = 4-dimethylaminopyridine.

Scheme 2 Results of the Cu-catalyzed conjugate addition of $ZnEt_2$ to cyclohexenone in the presence of ligands **1**, **8** and **9**.

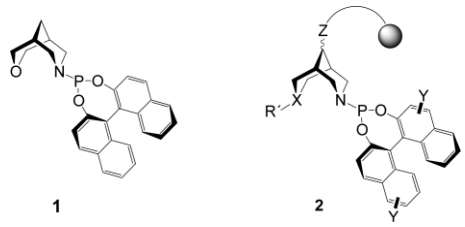


Fig. 1 Structure of ligand **1** and general structure of the ligand library **2**.

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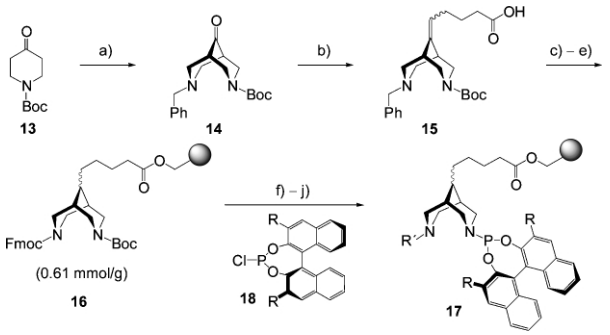
hydroxymethylpolystyrene (loading 0.61 mmol g^{-1}), and after selective removal of the Fmoc group the liberated secondary amine was modified by means of acylation-, (thio)isocyanation, reductive amination-, alkylation-, phosphorylation- or sulfonylation reactions (Scheme 3).

All transformations were investigated in solution with a model bispidine first and then transferred to the solid phase. Finally, after removal of the Boc group the second amino group was converted into a phosphoramidite with substituted chlorophosphites **18**. By analogy, phosphoramidites were synthesized embodying an oxa-, thia- or carba-bispidine system or a piperidine core. The building blocks employed for the library synthesis are shown in Fig. 2.

After completion of the synthesis the ligands were converted into the corresponding polymer-bound copper complexes as described above and investigated by 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 M HCl and the enantiomer ratio



Scheme 3 Synthesis of polymer-bound ligands **17**: (a) $PhCH_2NH_2$, $(HCHO)_n$, AcOH, MeOH, 65 °C, 4 h, 81%; b) $Br^- Ph_3P^+(CH_2)_4COOH$, KO*t*Bu, THF, 0 °C → rt, 2.5 h, 68%; (c) H_2, Pd/C, EtOH, 12 h, rt; (d) FmocCl, $NaHCO_3$, THF, H_2O, 12 h, rt, 69% (2 steps); (e) hydroxymethylpolystyrene, DIC, DMAP, CH_2Cl_2, 12 h, rt, 94% (0.61 mmol g^{-1}), then Ac_2O, pyridine, CH_2Cl_2; (f) piperidine, DMF; (g) introduction of the N-substituent (see text); (h) TFA, CH_2Cl_2; (i) Et_3N, CH_2Cl_2; (j) ClP(R_2BINOL) **18**, Et_3N, toluene; DIC = *N*,*N*′-diisopropylcarbodiimide, BINOL = 2,2′-dihydroxy[1,1′]binaphthyl.

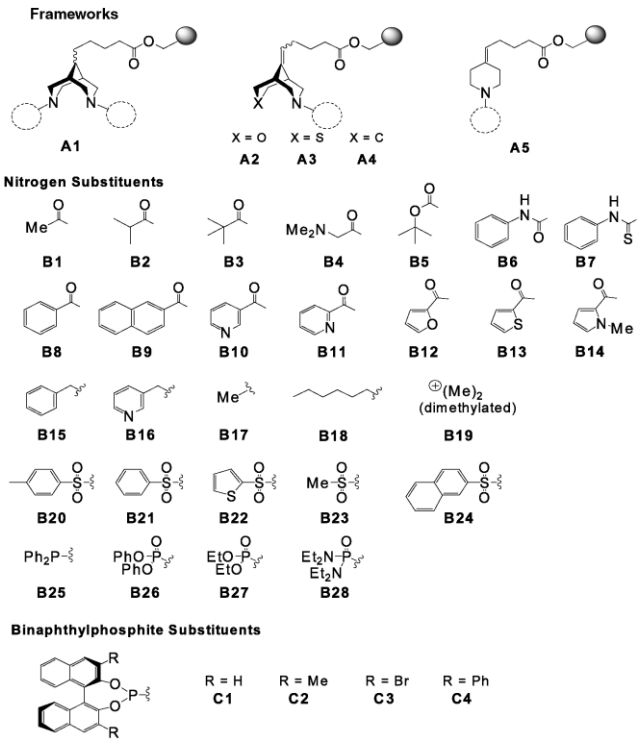


Fig. 2 Building blocks used in the library synthesis.

was determined without further separation procedures by means of gas chromatography employing a chiral stationary phase.[8]

The ligands were screened in two rounds of investigation. In the first round bispidine core **A1** and unsubstituted binaphthylphosphite **C1** were employed and the modulating substituents **B1**–**B28** at the second nitrogen atom were varied. The results are given in Fig. 3. 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 the sterically demanding pivaloyl amide **B3** (44% ee) the stereoselectivity was significantly higher than with an acetamide **B1**. Weakly complexing aromatic substituents like the thiophene system **B13** (38% ee) were much better than pyridine heterocycles (**B10**, **B11**), and also *N*-alkyl groups were not advantageous (**B15**–**B18**). On the other hand, in particular the phosphoryl (**B26**, 50% ee) and the 4-tosyl group **B20** (56% ee) gave very encouraging results.

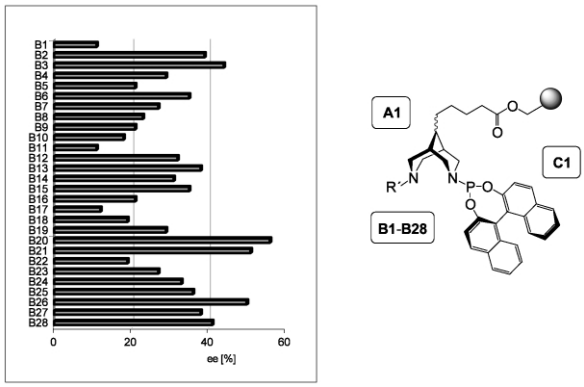


Fig. 3 Results of the first screening round.

Based on these results, ligands embodying the most promising N-substituents were subjected 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 analogs **A2**–**A5**. The results of the corresponding enantioselective conjugate additions are shown in Fig. 4. 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 to 67% ee. A similar observation is made for the thiophenoylamide (**A1**–**B13**–**C1/C2**) (45% ee). Interestingly this trend is reversed for the ligands embodying a sulfonyl- (**A1**–**B20**–**C2**, 46% ee) or a diphenylphosphoryl group (**A1**–**B26**–**C2**, 41% ee). Pronounced, albeit different cooperative effects between the two substituents of the nitrogen atoms are also apparent from further combinations, compare for instance **A1**–**B3**–**C3/C4** with **A1**–**B13**–**C3/C4**. We would like to stress that the most advantageous

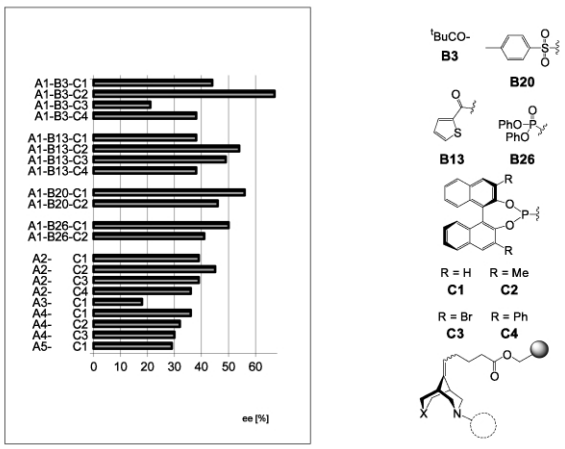
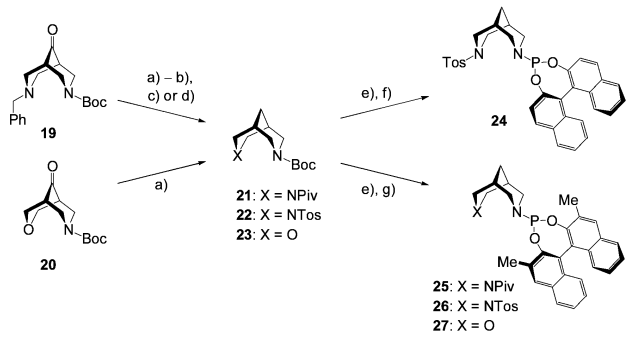


Fig. 4 Results of the second screening round.

modulating N-substituent identified in the first screening round, *i.e.* the 4-tosyl-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',[2a,b] optimising 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.

In order to validate the screening of the solid-phase bound ligands and to compare the recorded results with the corresponding reactions in homogeneous solution, ligands **24–27** were synthesized as shown in Scheme 4.



Scheme 4 Synthesis of ligands **24–27**: (a) $TosNHNH_2$, TosOH, $NaCNBH_3$, DMF, 2 h, 100 °C, 48%; (b) H_2, Pd/C, EtOH, 12 h, rt; (c) Piv_2O, DMAP, pyridine, 12 h, rt, 71% (**21**, 2 steps); (d) TosCl, DMAP, pyridine, 12 h, rt, 72% (**22**, 2 steps); (e) TFA, CH_2Cl_2, 30 min, rt; (f) ClP(BINOL) **10**, Et_3N, toluene, 12 h, rt, 51% (**24**); (g) PCl_3, Et_3N, THF, 1 h, 0 °C; then 3,3′-dimethyl-2,2′-dihydroxy[1,1′]binaphthyl, Et_3N, THF, 12 h, rt, 30% (**25**), 12% (**26**) and 3% (**27**), respectively; Piv = pivaloyl, Tos = toluene-4-sulfonyl.

To this end, bispidinones **19** and **20** were converted into Boc-protected intermediates **21–23**. After removal of the Boc group the liberated secondary amine was phosphitylated. Phosphoramidite **24** was obtained readily by reaction with chlorophosphite **10**. In the cases of methyl-substituted phosphoramidites **25–27** subsequent treatment of the secondary amine with PCl_3 and the dimethyl-substituted binaphthol gave better results.

In Table 1 the enantioselectivity recorded in the Cu-catalyzed conjugate addition of diethylzinc to cyclohexenone in the presence of soluble ligands **24–27** and **1** is compared with the values determined in the presence of the corresponding polymer-bound ligands. In all cases the ee-values are very similar, the maximum deviation reaching only 5% ee. Thus, the combinatorial ligand development and screening system employing immobilized heterogeneous catalysts provides a correct picture of the corresponding situation for the enantioselective conjugate addition reactions in homogeneous solution.

Table 1 Comparison of polymer-bound and corresponding soluble ligands

Entry[a]	Ligand type	BINOL-substituent	Heterogeneous[a] ee[b] [%] (ligand)	Homogeneous[a] ee[b] [%] (ligand)
1	Oxa-	H	39 (**A2–C1**)	43 (**1**)
2	Bispidine	Me	45 (**A2–C2**)	47 (**27**, 1 mol%)
3	*N*-	H	44 (**A1–B3–C1**)	Not determined
4	Pivaloyl-	Me	67 (**A1–B3–C2**)	64 (**25**)
5	*N*-Toluene	H	56 (**A1–B20–C1**)	56 (**24**)
6	4-Sulfonyl	Me	46 (**A1–B20–C2**)	51 (**26**)

[a] Conversion in all cases >95%; isolated yields >90%; [b] Determined by means of gas chromatography (Lipodex E, Macherey&Nagel); the (*R*)-enantiomer was formed predominantly in all cases.

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