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Synthesis and application in asymmetric C–C bond formation of solution phase ligand libraries of monodentate phosphoramidites†

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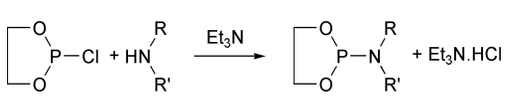
A library of 96 unique monodentate phosphoramidite ligands has been synthesized in solution and used in the asymmetric conjugate addition of potassium vinyltrifluoroborate to enones resulting in up to 88% ee.

Combining enantioselective homogeneous catalysis and combinatorial chemistry in an efficient way is a highly desirable goal since it leads to the rapid discovery of new catalysts for important asymmetric transformations.[1] However, combinatorial approaches are often based on mixtures of compounds,[2] whereas asymmetric catalysis requires the ability to individually detect the activity and selectivity of each catalyst in a library. Parallel reactions (one catalyst per vial),[3] followed by high-throughput screening,[4] has emerged as the method of choice combining these two fields. Impressive results have been obtained using solid-phase bound ligand libraries.[5] However, the translation of solution phase chemistry to the solid-phase and *vice versa* can be quite problematic, as illustrated by recent examples employing solid-phase bound phosphoramidite ligands.[6] We focused on an automated solution phase parallel synthesis of phosphoramidite libraries, since it allowed the preparation of libraries (up to 96 members) in sufficient quantities using existing methodology. Phosphoramidites can be easily obtained by the reaction of a phosphorochloridite with a primary or secondary amine in the presence of triethylamine as a base. The modular structure makes them highly suitable for synthesis in a combinatorial way (Scheme 1).[7]



Scheme 1 Phosphoramidite ligand synthesis.

The automation of the synthesis is achieved by using all reagents as stock solutions, which are transferred by a liquid handling robot placed in a glove box.[8] The chromatography normally performed at the end of the phosphoramidite synthesis, is replaced by a simple filtration, not only because it allows for a much more simple automated procedure, but also because phosphoramidites based on primary and/or aromatic amines tend to decompose during chromatography. For the parallel synthesis of the 96 ligand library according to Fig. 1, toluene stock solutions of the three BINOL-based phosphorochloridites (Scheme 2) were added to a 96-well oleophobic filterplate in three areas of 32 wells respectively (Fig. 1).

The addition of a stoichiometric amount of triethylamine to each of the 96 wells was followed by the addition of a stoichiometric amount of 32 different amines (Table 1) to each area

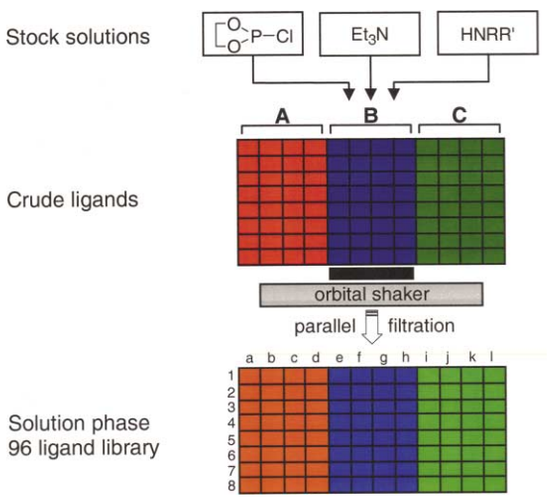
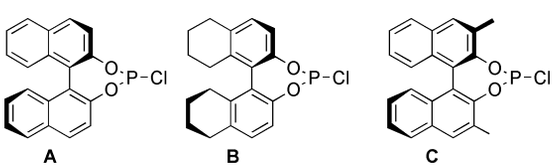


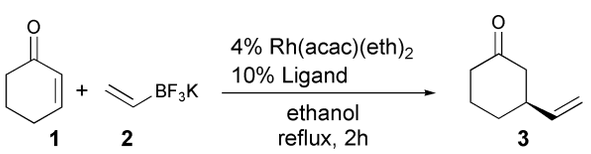
Fig. 1 Library synthesis.



Scheme 2 Phosphorochloridites used.

containing phosphorochloridites **A–C**, giving 96 different crude phosphoramidites based on three diols and 32 amines.

After two hours of agitation at room temperature on an orbital shaker, the precipitated triethylamine hydrochloric acid salts were removed *via* parallel filtration. By placing the oleophobic filterplate on top of a 96-well microplate and applying vacuum, a library of 96 clear stock solutions of phosphoramidites in toluene was obtained. ^{31}P-NMR demonstrated that the ligands were formed with >90% purity. The ligand library was subsequently screened in the asymmetric conjugate addition of potassium vinyltrifluoroborate (**2**) to cyclohexenone (**1**) (Scheme 3).[9] The introduction of a vinyl-group in an enantioselective fashion using a monodentate phosphoramidite ligand is highly desirable since versatile synthons are produced, which up to now have only been obtained using Rh-BINAP catalysts.[10]



Scheme 3 Asymmetric conjugate addition of vinyltrifluoroborate.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/ob/b4/b404996a

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Table 1 Amines used

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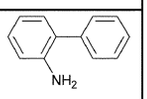
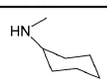
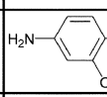
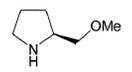
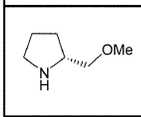
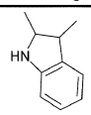
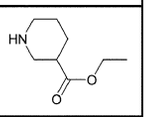
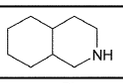
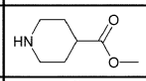
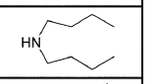
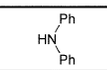
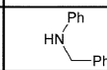
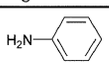
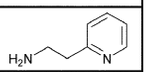
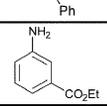
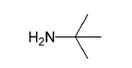
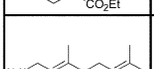
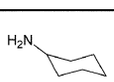
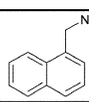
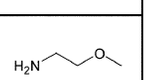
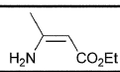
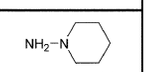
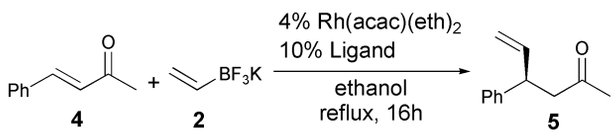
1				
2				
3				
4				
5				
6				
7				
8				

Using the liquid handling robot, a part of the entire solution phase library was transferred to 96 corresponding reaction vials, followed by a stock solution of the rhodium source and substrate **1** in ethanol. After the addition of trifluoroborate **2** the vials were sealed, placed in a Premex 96-Multi Reactor,[11] and heated at reflux for two hours. In order to allow a structure–activity and structure–selectivity analysis a short reaction time (2 h) was used whereby the reactions did not run to completion and a broad range of conversions and ee values is obtained. Analysis by chiral GC gave the results shown in Fig. 2.

All the ligands based on the 3,3′-dimethyl-BINOL backbone (**C**) give low conversions and ee values, with the phosphoramidite based on aniline as the best ligand (21% conv., 50% ee).[12] The BINOL (**A**) based phosphoramidites perform much better, and the 8H-BINOL[13] (**B**) based ligands even improve these results. Ligands based on primary aromatic amines lead to low conversions (5–39%) and ee values (11–37%). The most successful ligands are based on 8H-BINOL and secondary aliphatic amines like ethylmethylamine (Fig. 2, 8e, 80% conv., 82% ee) and diethylamine (Fig. 2, 1f, 81% conv., 87% ee). To validate the results these two ligands were synthesized individually on a larger scale, including purification by column chromatograghy. The results correspond neatly with the ones from the solution phase library (96% conv., 86% ee for 8e and 99% conv., 88% ee for 1f) demonstrating the potential of this concept. Next to a cyclic enone, the acyclic enone benzylidene acetone (**4**) was also used a substrate in the screening of the library (Scheme 4).



Scheme 4 Conjugate addition to benzylidene acetone.

The reaction was run overnight and conversion and ee determined by chiral GC. The results are shown in Fig. 3.

As in the case of cyclohexenone, the BINOL (**A**) and 8H-BINOL (**B**) based phosphoramidites perform much better than the 3,3′-dimethyl-BINOL (**C**) based ligands; the latter giving conversions up to only 22% and ee values up to 29% (Fig. 3, 4l). The most effective ligands, showing high conversion although moderate ee so far, are based on cyclic amines containing ester substituents (3d, 3h, and 4b with ee values of 42%, 40%, and 41%, respectively).

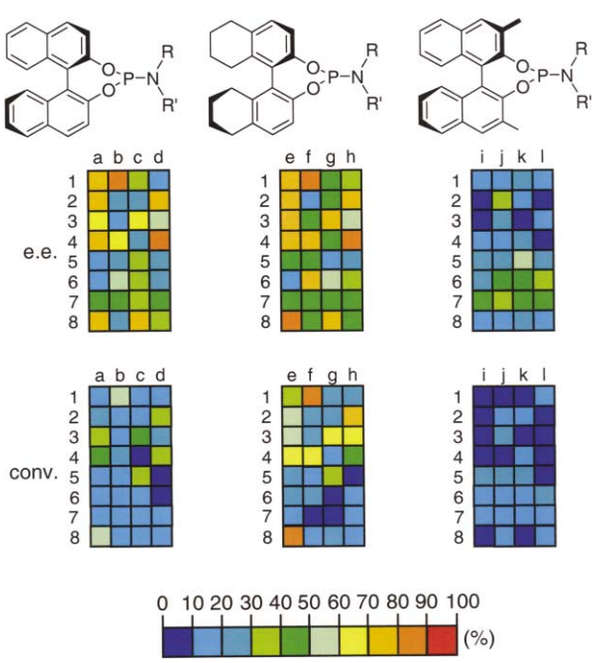


Fig. 2 Results of the library screening for the 1,4-addition of **2** to **1** (ee upper row, conversion lower row).

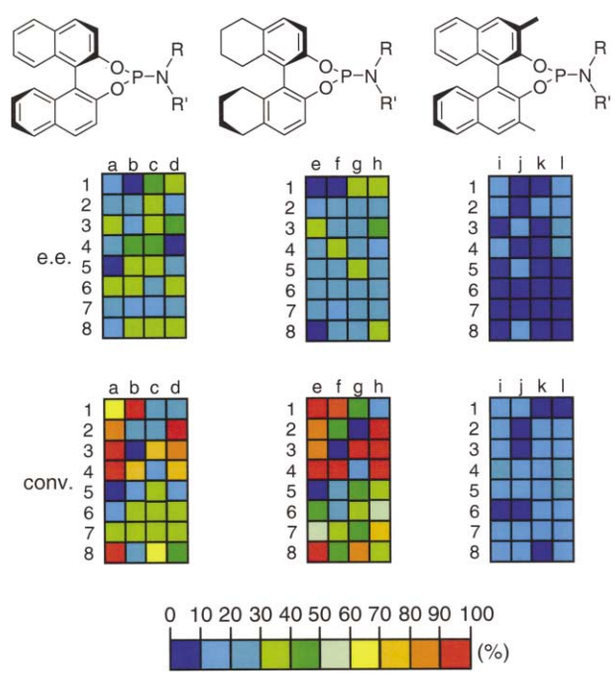


Fig. 3 Results of the library screening for the 1,4-addition of **2** to **4**.

In summary we have shown that solution phase libraries of chiral monodentate phosphoramidite are rapidly synthesized and screened in asymmetric C–C bond forming reactions using an automated parallel protocol. This method leads to the quick discovery of (leads for) effective enantioselective catalysts for various transformations and, in association with the monodentate ligand combination approach recently introduced,[14] provides a powerful tool for combinatorial asymmetric catalysis.

Acknowledgements

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