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Instant Ligand Libraries. Parallel Synthesis of Monodentate Phosphoramidites and in Situ Screening in Asymmetric Hydrogenation

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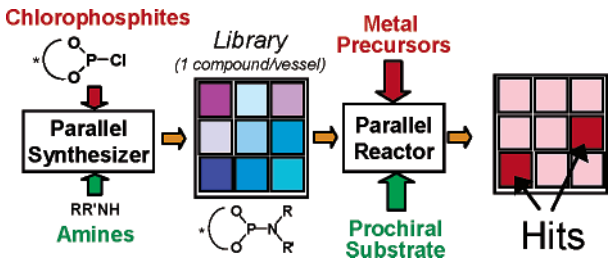
ABSTRACT



Chiral phosphoramidites have been identified as excellent ligands for various metal-catalyzed enantioselective transformations. Taking advantage of their easy preparation and modular nature, we designed a fully automated protocol for the parallel preparation of a library of 32 phosphoramidites and its screening in asymmetric hydrogenation of amino acid precursors. This initial study led to the discovery of a new ligand for the preparation of an enantiopure β^3-homoalanine precursor.

Rapid synthesis and screening of chiral ligands is an efficient method for finding enantioselective transition-metal catalysts, especially in an industrial environment where time-to-market constraints are severe.[1] To date, most ligand libraries have been synthesized one at a time, as they can be prepared only by multistep syntheses requiring purification. Automation has been used in the synthesis of libraries of ligands on solid phase. However, the presence of the polymer can have a detrimental effect on the rate and the selectivity when screening is performed on the bead.[1,2]

The easy preparation and the modular nature of the chiral phosphoramidites make them ideally suited for a parallel synthesis approach. Several compounds of this class have been identified as excellent ligands for various enantioselective transformations.[3] It is important to note that, for the enantioselective reactions investigated so far, a different member of the phosphoramidites class is often required to obtain the best catalyst.

Herein, we report a very fast protocol for the automated solution-phase synthesis of a library of chiral phosphoramidites and the screening of this library in the enantioselective hydrogenation of amino acid precursors.

Phosphoramidites are easily obtained by reaction between a chlorophosphite and a primary or secondary amine in the presence of a base.[3a] Chlorophosphites are prepared in a one-step reaction between excess PCl_3 and a diol. In the case of enantiomerically pure 2,2′-binaphthol and its analogues, the

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(2) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217.

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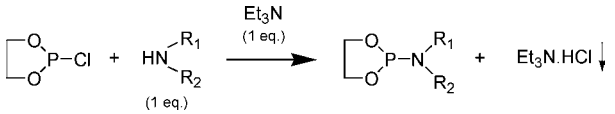
chlorophosphites can be isolated as solids. To obtain a pure phosphoramidite ligand, column chromatography and/or recrystallization were typically performed prior to its use in catalysis. This tedious workup represented an obstacle toward a fully automated preparation of a large ligand library.

Considering Scheme 1, one realizes that as long as stoichiometric amounts of reagents are used and the reaction

Scheme 1. Synthesis of Phosphoramidite Ligands



goes to completion, the main impurity present is the HCl salt of the base. Thus, performing the reaction in a suitable solvent followed by simple filtration of the precipitated HCl salt should lead to sufficiently clean phosphoramidite ligands. To verify this idea, a known phosphoramidite (derived from (*R*)-2,2′-binaphthol and diethylamine)[4] was synthesized according to this simplified protocol and tested in the Rh-catalyzed hydrogenation of methyl *2*-acetamidocinnamate (**1**). Remarkably, the conversion and the ee obtained (full conversion, ee of 94%) were similar to the values obtained with purified ligands (full conversion, ee of 97%).[5] No filtration led to an inactive catalyst. The simplified synthetic protocol could then be easily automated by using a 96-well oleophobic filterplate. Parallel filtration is performed upon application of vacuum, and the filtrates are collected in a second 96-well microplate that can be used for storage (Figure 1).

Our first library of ligands contained 32 members (Figure 2). It was prepared by reacting (*R*)-2,2′-binaphthol-based chlorophosphite with 32 different amines in the presence of triethylamine as a base, thus generating 32 phosphoramidites with a wide diversity in their amino moiety. This initial set of amines was randomly assembled to validate the concept. It contained 24 primary amines and 8 secondary amines. Primary amines have not been used extensively as they lead to phosphoramidites that partially decompose during purification. The absence of the purification step in the automated procedure makes these primary amine based phosphoramidites readily available.

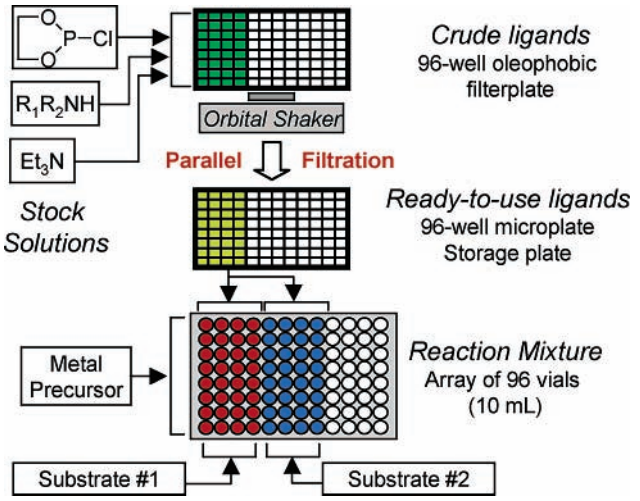


Figure 1. Protocol for the synthesis of the library.

Stock solutions of all the reagents were prepared in toluene and dispensed directly into the 96-well microplate with a liquid handling robot. The 32 reaction mixtures were vortexed using an orbital shaker for 2 h followed by parallel filtration giving 32 ligand solutions. A fraction of each solution was transferred to two sets of 32 vials, which contained $Rh(COD)_2BF_4$ (L/Rh ratio = 2 mol/mol) and substrate **1** in DCM and *Z*-methyl 3-acetamido-2-butenoate (**2**) in *i*-PrOH, respectively (substrate/Rh = 50 mol/mol, Figure 1). The 64 hydrogenation reactions were performed in parallel in a Premex 96-Multi Reactor[6] at room temperature and 6 bar of H_2 for 1 h. The results are presented in Figure 2.

For the set using substrate **1**, almost all of the members of the library led to full conversions, indicating that most of the ligands were formed with an acceptable degree of purity. ^{31}P NMR revealed the presence of trace amounts of other phosphorus species that remarkably did not affect the performance of the catalyst. The absence of reaction for the phosphoramidites based on **4B** and **6C** was due to the nonformation of the ligand, as observed by NMR. This gives an acceptable cull rate (ratio of failed syntheses over the total number of compounds) for the library of ~10%. The most enantioselective ligands for this reaction are based on secondary amines, i.e., **7A**, **7B**, **7C**, and **8A** with ee's of 94%, 95%, 91%, and 92%, respectively. The ee's are slightly lower than those obtained with fully purified ligands but the ranking is in agreement with previous results.[3c,d,4,5]

Results with the more challenging substrate **2** are far less uniform. In terms of enantioselectivities, the best ligands are all based on primary aliphatic amines branched on the α-carbon (e.g., **1B**, 92% ee; **1C**, 92% ee; **2B**, 94% ee; **5C**,

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(4) Jia, X.; Li, X.; Xu, L.; Shi, Q.; Yao, X.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 4539.

(5) See the Supporting Information.

(6) This reactor was developed by Premex in cooperation with DSM. See: www.premex-reactorag.ch/e/spezialloesungen/produkteneuheiten/.

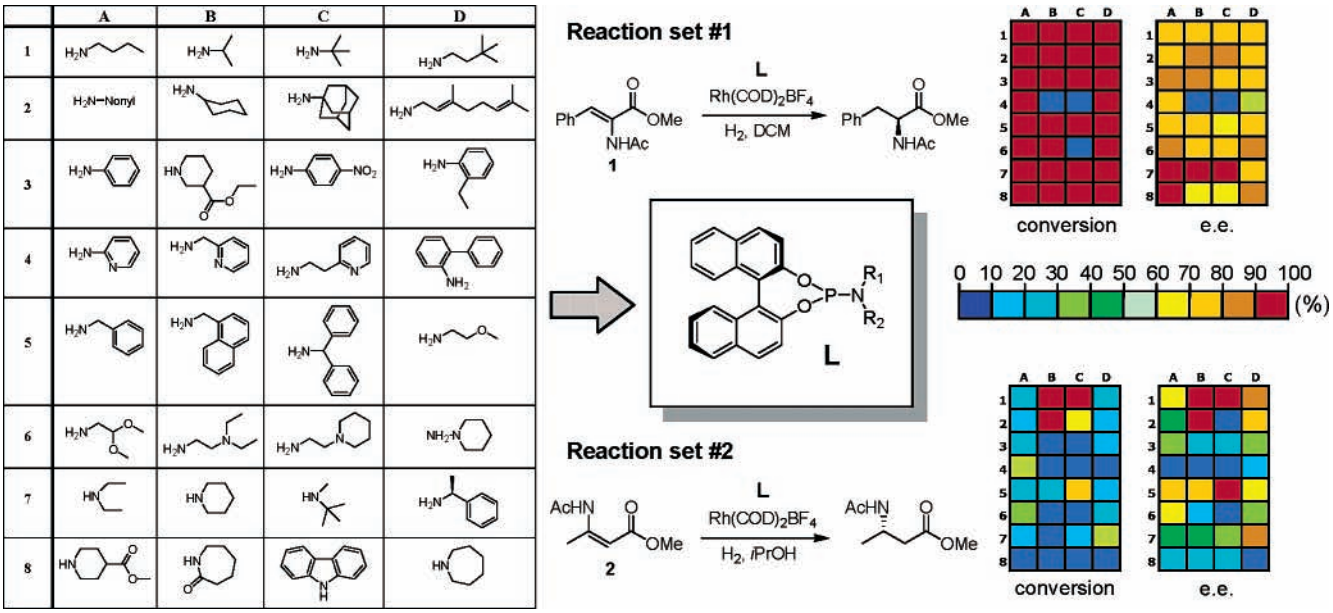

Figure 2. Set of amines used to synthesize the phosphoramidites library and results obtained in the Rh-catalyzed hydrogenation of amino acid precursors.

96% ee; **7D**, 88% ee). However, differences in activity can be observed within this set of ligands. Whereas **1B**, **1C**, and **2B** give full conversion, the conversions using **5C** and **7D** are only 72% and 51%, respectively, indicating that the presence of a phenyl ring is slowing down the reaction.[7] Phosphoramidites based on secondary amines or primary amines lacking the α-carbon branching (e.g., **5A**, 28% conversion, 73% ee) do not perform well in this hydrogenation. The phosphoramidite with **1B** as an amino moiety was prepared and tested on a larger scale, giving the best results obtained, thus far,[3e] for this particular substrate (estimated T.O.F.: 150 h^{-1}, 95% ee).

In conclusion, we have developed a protocol for the rapid synthesis of a library of phosphoramidite ligands that can be used without further purification in asymmetric hydrogenation. This protocol allows the preparation of 96 phosphoramidites within 1 day and the screening of the library for at least three desired asymmetric hydrogenations during the next day.[8] Storage and reuse of the library is also possible. There are large cost savings associated with the use of this method in industry. In academia, its use greatly enhances the chances of finding interesting new catalytic reactions, as it frees the researcher from repetitive work. We believe that this advanced screening method can be extended to other catalytic applications and will greatly promote the use of homogeneous catalysis in the production of fine chemicals.

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Supporting Information Available: Experimental procedures and quantitative results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) We expect that this method can be easily extended to the monodentate phosphonites (Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961) and phosphites (Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889).