Synthesis of Solution-Phase Phosphoramidite and Phosphite Ligand Libraries and Their In Situ Screening in the Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids

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Received December 14, 2006

Herein, we report the automated parallel synthesis of solution-phase libraries of phosphoramidite ligands for the development of enantioselective catalysts. The ligand libraries are screened in situ in the asymmetric rhodium-catalyzed addition of arylboronic acids to aldehydes and imines. It is shown that the described methodology results in the straightforward discovery of leads for highly efficient enantioselective catalysts.

Introduction

The identification of suitable catalysts for asymmetric synthesis poses a significant problem in contemporary chemistry. Current mechanistic knowledge, although far advanced, mostly, does not allow the de novo "design" of catalysts that will display high enantioselectivity. Subtle variations in ligand structure, corresponding to minute differences in transition state energy ($\Delta\Delta G^{\ddagger} \cong 1-2$ kcal mol^{-1}), can cause significant changes in enantioselectivity.[1] Moreover, the degree of structural recognition that is a prerequisite for highly selective catalysts often precludes selectivity for a broad range of substrates. Currently, the development of efficient catalysts for asymmetric synthesis is largely empirical and often a result of knowledge-based intuition or serendipity. Flexible ligand synthesis strategies, in which several analogues of a promising ligand-type are prepared, appear to be an especially fruitful strategy in this area. However, the synthetic procedures for chiral ligands are often lengthy and unsuitable for such an approach. There is a clear need for a more methodical approach in which the catalyst, that is, the ligand, is systematically varied. A combinatorial approach for the rapid development of new catalysts for asymmetric transformations is highly desirable.[2] Such an approach also allows for the identification of an optimal catalyst for each particular class of substrates, thus overcoming the problem of generality that arises when only a small number of chiral catalysts are available. Parallel reactions using one catalyst, although not necessarily one substrate,[3] per vial,[4] combined with high-throughput screening,[5] has emerged as the method of choice for the combination of these two fields.[6]

Although impressive results have been obtained with solid-phase-bound ligand libraries,[7] the translation of this chemistry to solution phase can be quite problematic. Parallel synthesis of asymmetric catalysts is, therefore, mostly performed in solution. Chiral ligands, employed in a parallel synthesis/screening approach, require a modular buildup with easily connectable components. From an industrial perspective, where successful catalytic procedures will be scaled up, the ligands should also be cost effective when produced in larger quantities.[1a]

After a seminal report of Gilbertson et al. on the synthesis of modular ligand libraries of phosphane-containing peptides for asymmetric hydrogenation,[8] several reports have appeared concerning the parallel synthesis of ligand libraries for asymmetric catalysis. Amino acid building blocks[9] are a popular choice in initial explorations at the interface of combinatorial chemistry and asymmetric catalysis.[10] Apart from the Gilbertson work, very few groups have reported the parallel synthesis of phosphorus-containing ligands.[11] A recently developed strategy that takes the use of monodentate ligand libraries one step further is the use of ligand mixtures. This can be done either as such[12] or in a supramolecular fashion.[13]

Monodentate phosphoramidite ligands have proven to be highly successful in a wide variety of copper-,[14] iridium-,[15] palladium-,[16] and rhodium-catalyzed[17] enantioselective reactions. However, a different member of the ligand family is required for most of these reaction types and often even within a reaction type for individual substrate classes. The modular buildup of phosphoramidite ligands makes them highly suitable for a combinatorial approach. Recently, Lefort et al. reported the automated parallel synthesis and in situ screening of libraries of monodentate phosphoramidite ligands in rhodium-catalyzed hydrogenation reactions (Figure 1).[18] The protocol allows for the parallel preparation of a

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10.1021/cc060161k CCC: $37.00
Published on Web 04/13/2007

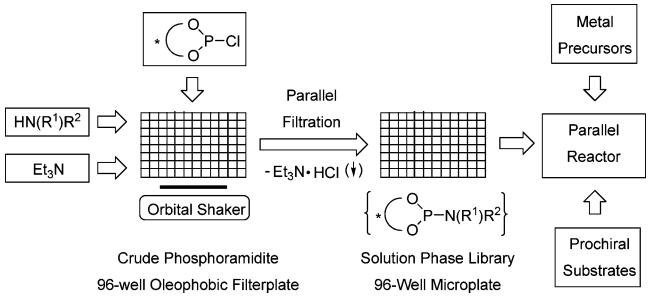


Figure 1. Parallel preparation of a solution-phase library of phosphoramidites in a 96-well format in 1 day and their subsequent in situ parallel screening.

solution-phase library of phosphoramidites in a 96-well format in 1 day and their subsequent in situ parallel screening. Our group recently used this novel technology for the effective screening of a library of phosphoramidites in the rhodium-catalyzed conjugate addition of vinyltrifluoroborates to cyclic and acyclic enones, screening 96 ligands on two substrates in one run.[16f] Encouraged by the results obtained in this research, we decided to expand this technique to the discovery of new catalysts in related transformations.

Because of their importance as intermediates for the synthesis of biologically active compounds,[19] the enantioselective formation of chiral diarylmethanols and diarylmethylamines has attracted a great deal of interest.[20] An attractive route to these compounds is the catalytic asymmetric addition of aryl organometallic reagents to aryl aldehydes and imines.[21] Boron reagents have received increasing attention as arylating reagents because they are readily available, stable, and compatible with a large variety of functional groups.[22] In 1998, Miyaura and co-workers demonstrated the rhodium-catalyzed addition of arylboronic acids to aromatic aldehydes under conditions similar to those used for the conjugate addition to enones.[23] In an asymmetric version of this reaction, employing MeO−MOP as chiral ligand, 41% ee was achieved for the addition of phenylboronic acid to 1-naphthaldehyde. Until recently,[24] attempts to improve the enantioselectivity of this reaction remained unsuccessful.[25] The development of a suitable chiral ligand for this transformation is still a major goal.

In contrast to the addition of aldehydes, high enantioselectivities have been obtained in the rhodium-catalyzed arylation of aryl imines. Excellent ee values have been achieved for the addition of arylstannane[26] and aryltitanium reagents.[27] In 2004, Tomioka and co-workers described the first enantioselective addition of arylboronic acids and their boroxine trimers to *N*-tosyl-activated benzaldimines.[28] Enantioselectivities above 90% were obtained through steric tuning of the substituents on both the substrate and the boron reagent. Hayashi and co-workers reported excellent enantioselectivities for the addition of arylboroxines to *N*-tosyl- and *N*-nosyl-activated benzaldimines employing chiral diene ligands.[29] However, the removal of the tosyl and nosyl activating/protecting groups is either not straightforward[30] or requires environmentally unfriendly reagents.[28b] Ellman and co-workers reported an example of high enantioselectivity for the addition of arylboronic acids to benzaldimine using DeguPHOS as a chiral ligand. The authors presented the easily removable *N*-diphenylphosphinoyl group as an alternative to the aforementioned sulfonyl groups.[31]

Recently, our group developed the highly efficient, microwave-assisted deprotection of the *N*,*N*-dimethylsulfamoyl group.[32] We envisioned that the use of this inexpensive, low-molecular-weight group, in combination with a rhodium-phosphoramidite catalyst, would lead to a more efficient and synthetically versatile system.[33] Herein, we report the successful application of in situ prepared first and second generation libraries of phosphoramidite ligands in the development of enantioselective catalysts for the 1,2-addition of arylboronic acids using both arylaldehydes and *N*,*N*-dimethylsulfamoyl-protected arylaldimines as substrates.[23a,32]

Results and Discussion

Solution-Phase Libraries of Phosphoramidite Ligands in the Development of a Catalyst for the Enantioselective Synthesis of Diarylmethanols. Preliminary studies were carried out for the rhodium-catalyzed 1,2-addition of phenylboronic acid to *p*-chlorobenzaldehyde **1** (Table 1). Different solvents were examined, of which 2-propanol appeared to be the most suitable solvent for this reaction, increasing both reactivity and enantioselectivity. A solution-phase library of 28 ligands **L1**{*x*} was readily obtained by an automated synthesis starting from primary and secondary amines (Chart 1) and phosphorochloridite **2** (Scheme 1, $R^1 = R^2 = H$), which is readily prepared from BINOL and an excess of PCl_3.[34]

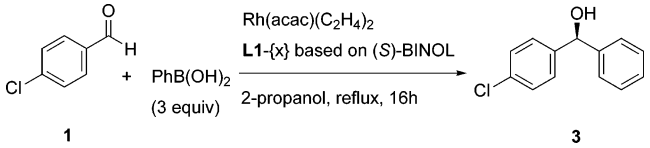
To create a ligand library that will be suitable for lead-finding purposes, a selection of structurally different amines was made that provides a variety of steric and electronic properties. In addition to monodentate ligands, two bidentate ligands were prepared using diamines. With a liquid handling robot, toluene stock solutions of the phosphorochloridite, amines, and triethylamine were dispensed directly into a 96-well oleophobic filter plate. The vials were vortexed for 2 h, after which the precipitated triethylammonium chloride was removed via parallel filtration into a 96-well titer plate. The ligand solutions were transferred to a parallel reactor for in situ complexation with the $Rh(acac)(C_2H_4)_2$ precursor. After the addition of stock solutions of substrate **1** (0.1 mmol) and phenylboronic acid (3 equiv) in 2-propanol, the vials were sealed with screwcaps and heated overnight at reflux temperature.

Chiral HPLC analysis of the reaction mixtures showed that most of the ligands gave rise to enantioselectivities below 40% and therefore did not exceed the results obtained by Miyaura (Table 1).[21] However, the monodentate ligands **L1**{*20*} and **L1**{*22*} provided 47 and 51% ee, respectively. Also bidentate ligand **L1**{*27*} provided product **3** in 51% ee. Interestingly, the bidentate ligands based on (*S*)-BINOL provided the R enantiomer of the product, whereas the monodentate ligands provided the S enantiomer.

To establish the validity of our protocol, the results of 16 representative library ligands were compared with the corresponding phosphoramidite ligands that were synthesized manually and purified by column chromatography (Table 2).

In general, the enantioselectivities provided by the monodentate members of the (unpurified) solution-phase library

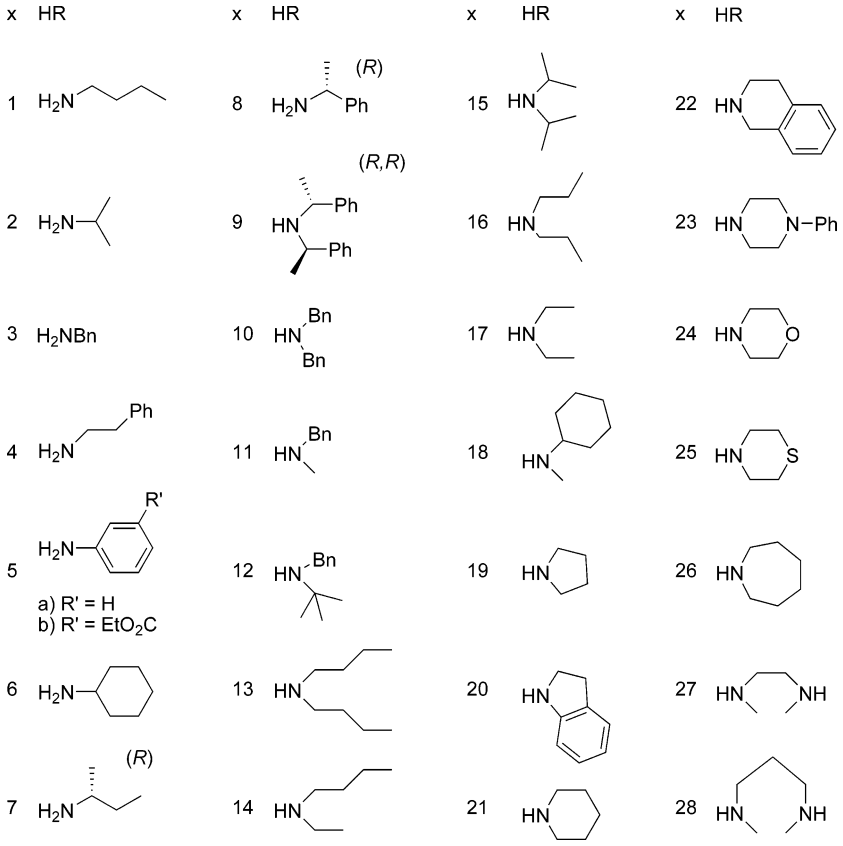
Table 1. Enantioselectivities Obtained in the In Situ Screening of Solution-Phase Library **L1**{*x*}for the Phenylboronic Acid Addition to Benzaldehyde **1**[a]



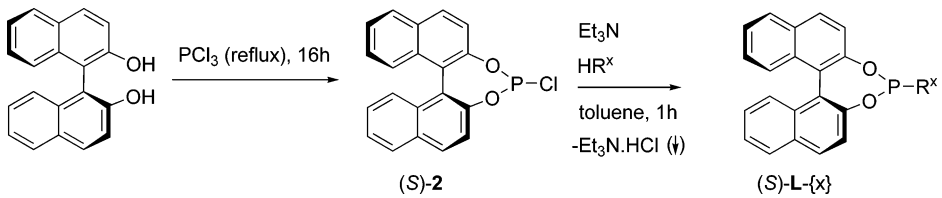
L1{*x*}	ee[b,c]	**L1**{*x*}	ee[b,c]	**L1**{*x*}	ee[b,c]	**L1**{*x*}	ee[b,c]
L1{*1*}	17% (*S*)	**L1**{*8*}	20% (*S*)	**L1**{*15*}	28% (*S*)	**L1**{*22*}	51% (*S*)
L1{*2*}	19% (*S*)	**L1**{*9*}	16% (*S*)	**L1**{*16*}	20% (*S*)	**L1**{*23*}	15% (*S*)
L1{*3*}	28% (*S*)	**L1**{*10*}	18% (*S*)	**L1**{*17*}	33% (*S*)	**L1**{*24*}	29% (*S*)
L1{*4*}	20% (*S*)	**L1**{*11*}	27% (*S*)	**L1**{*18*}	21% (*S*)	**L1**{*25*}	28% (*S*)
L1{*5a*}	32% (*S*)	**L1**{*12*}	25% (*S*)	**L1**{*19*}	27% (*S*)	**L1**{*26*}	21% (*S*)
L1{*6*}	27% (*S*)	**L1**{*13*}	21% (*S*)	**L1**{*20*}	47% (*S*)	**L1**{*27*}	51% (*R*)
L1{*7*}	18% (*S*)	**L1**{*14*}	32% (*S*)	**L1**{*21*}	28% (*S*)	**L1**{28}	19% (*R*)

[a] Reactions were carried out on 0.1 mmol scale in the presence of a catalyst generated from 5 mol % Rh(acac)$(C_2H_4)_2$ and 12.5 mol % of monodentate phosphoramidite or 6.25 mol % of bidentate phosphoramidite. [b] Enantioselectivities were determined by chiral HPLC of the reaction mixtures. [c] The absolute configuration was established by comparison of the optical rotation with literature values.

Chart 1. Amines Used in the Preparation of Primary Solution-Phase Ligand Library **L1**{*x*}



Scheme 1. Divergent Synthesis of BINOL-Based Phosphoramidites



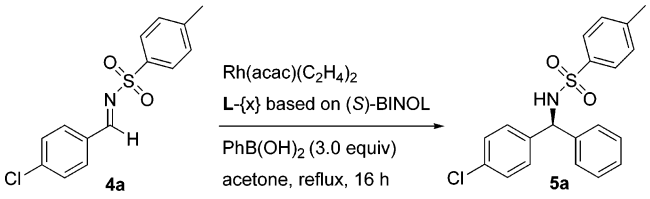
did not deviate more than 4% from the values obtained by the isolated ligands. Evaluation, however, of ligand **L1**{*12*} based on the bulky benzyl(*t*-butyl)amine gave a product with a significantly lower enantiomeric excess compared to the isolated ligand. ^{31}P NMR spectroscopy of **L1**{*12*} indicated incomplete formation of the ligand. Interestingly, ligands that were not fully formed in the library synthesis gave an orange-red solution upon addition of the rhodium source. In all other cases, the color of the catalyst solution was bright yellow, thus providing a color indication for the success of ligand

Table 2. Comparison of the Enantioselectivities Obtained with In Situ Prepared Phosphoramidite Ligands in the Solution-Phase with Those Obtained with Isolated Ligands [a]

L1{*x*}	Δee[b,c]	**L1**{*x*}	Δee[b,c]	**L1**{*x*}	Δee[b,c]	**L1**{*x*}	Δee[b,c]
L1{*8*}	1%	**L1**{*15*}	3%	**L1**{*20*}	1%	**L1**{*24*}	0%
L1{*10*}	0%	**L1**{*16*}	2%	**L1**{*21*}	1%	**L1**{*25*}	2%
L1{*12*}	11%	**L1**{*17*}	−2%	**L1**{*22*}	0%	**L1**{*26*}	3%
L1{*14*}	1%	**L1**{*19*}	3%	**L1**{*23*}	3%	**L1**{*27*}	9%

[a] Reactions were carried out on 0.1 mmol scale in the presence of a catalyst generated from 5 mol % Rh(acac)$(C_2H_4)_2$ and 12.5 mol % of monodentate phosphoramidite or 6.25 mol % of bidentate phosphoramidite. [b] Enantioselectivities were determined by chiral HPLC of the reaction mixtures. [c] Δee is calculated as the enantioselectivity obtained with isolated ligands minus the enantioselectivity obtained with the corresponding member of the solution-phase ligand library.

Table 3. Enantioselectivities Obtained in the In Situ Screening of Solution-Phase Library **L1**{*x*} for the Phenylboronic Acid Addition to Benzaldimine Substrate **4a**[a]



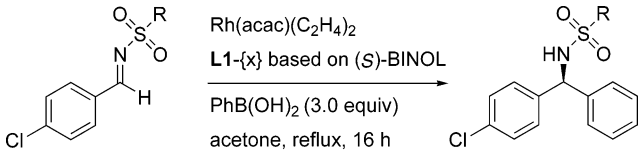
L1{*x*}	ee[b,c]	**L1**{*x*}	ee[b,c]	**L1**{*x*}	ee[b,c]
L1{*1*}	60% (*S*)	**L1**{*10*}	60% (*R*)	**L1**{*20*}	4% (*S*)
L1{*2*}	60% (*S*)	**L1**{*11*}	13% (*S*)	**L1**{*21*}	32% (*S*)
L1{*3*}	61% (*S*)	**L1**{*14*}	43% (*S*)	**L1**{*22*}	35% (*S*)
L1{*5a*}	60% (*S*)	**L1**{*16*}	21% (*R*)	**L1**{*23*}	16% (*R*)
L1{*5b*}	83% (*S*)	**L1**{*17*}	31% (*S*)	**L1**{*24*}	17% (*S*)
L1{*6*}	69% (*S*)	**L1**{*18*}	19% (*S*)	**L1**{*25*}	1% (*R*)
L1{*8*}	13% (*S*)	**L1**{*19*}	49% (*S*)	**L1**{*26*}	7% (*R*)

[a] Reactions were carried out on 0.1 mmol scale in the presence of a catalyst generated from 5 mol % Rh(acac)$(C_2H_4)_2$ and 12.5 mol % of monodentate phosphoramidite or 6.25 mol % of bidentate phosphoramidite. [b] Enantioselectivities were determined by chiral HPLC of the reaction mixtures. [c] The absolute configuration was established by comparison of the optical rotation with literature values.

formation.[35] The two bidentate members of the solution-phase library **L1**{*27*} and **L1**{*28*} were also not formed completely. To our surprise, the reaction with manually prepared ligand **L1**{*27*} went to full conversion within 4 h, providing the product with 60% ee instead of the 51% indicated by the solution-phase ligand library. After reaction of the first equivalent of phosphorochloridite with the diamine, the second amine functionality apparently competes with triethylamine for the formation of a salt with the liberated HCl. The resulting (monodentate) phosphoramidite salt is partly soluble in toluene and is, therefore, not completely removed upon filtration. This results in a mixture of bidentate and monodentate phosphoramidite ligands with a depletion in stereoselectivity by the monodentate ligands present. Therefore, although high reproducibility was shown for monodentate phosphoramidites, this methodology is not yet optimal for the exploration of bidentate ligands.

A study of the scope of bidentate ligand **L**{*27*}[23a] revealed that the rhodium/**L1**{*27*}-catalyzed phenylboronic acid addition to benzaldehydes is compatible with a wide range of functional groups. Enantioselectivities ranging from 50 to 75% were obtained using a range of electron-withdrawing and electron-donating substituents on the aryl moiety of the substrate. This catalyst, originating from the screening of one library, ranks therefore among the best for this reaction type.[36]

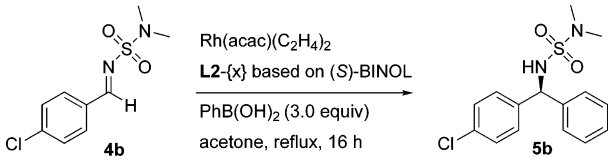
Table 4. Comparison of Enantioselectivities for Selected Ligands (*S*)-**L1**{*x*} in the Addition of $PhB(OH)_2$ to *N*-Tosyl-Protected Substrate **4a** and *N*,*N*-Dimethylsulfamoyl-Protected Substrate **4b**[a]



L1{*x*}	ee **5a**[b]	ee **5b**[c]	**L1**{*x*}	ee **5a**[b]	ee **5b**[c]
L1{*5a*}	60% (*S*)	62% (*S*)	**L1**{*21*}	32% (*S*)	48% (*S*)
L1{*5b*}	83% (*S*)	86% (*S*)	**L1**{*22*}	35% (*S*)	55% (*S*)
L1{*19*}	49% (*S*)	62% (*S*)	**L1**{*23*}	16% (*R*)	24% (*R*)
L1{*20*}	4% (*S*)	34% (*S*)	**L1**{*26*}	7% (*R*)	37% (*R*)

[a] Enantioselectivities were determined by chiral HPLC. Reactions were carried out overnight on a 0.1 mmol scale in 2 mL of acetone at reflux temperature using 3 equiv of phenylboronic acid in the presence of a catalyst generated from 3 mol % Rh(acac)$(C_2H_4)_2$ and 7.5 mol % of phosphoramidite. [b] Substrate **4a** was used. [c] Substrate **4b** was used.

Table 5. Enantioselectivities Obtained in the In Situ Screening of Secondary Solution-Phase Library **L2**{*x*} for the Phenylboronic Acid Addition to Benzaldimine Substrate **4b**[a]



L1{*x*}	ee (%)[b,c]	**L1**{*x*}	ee (%)[b,c]	**L1**{*x*}	ee (%)[b,c]
L1{*5c*}	83% (*S*)	**L1**{*5i*}	81% (*S*)	**L1**{*5o*}	84% (*S*)
L1{*5d*}	69% (*S*)	**L1**{*5j*}	85% (*S*)	**L1**{*5p*}	47% (*S*)
L1{*5e*}	62% (*S*)	**L1**{*5k*}	85% (*S*)	**L1**{*5q*}	48% (*S*)
L1{*5f*}	71% (*S*)	**L1**{*5l*}	78% (*S*)	**L1**{*5r*}	74% (*S*)
L1{*5g*}	80% (*S*)	**L1**{*5m*}	43% (*S*)	**L1**{*5s*}	25% (*S*)
L1{*5h*}	87% (*S*)	**L1**{*5n*}	79% (*S*)	**L1**{*5t*}	38% (*S*)

[a] Reactions were carried out on 0.1 mmol scale in 2 mL of solvent at reflux with 3 equiv of phenylboronic acid in the presence of a catalyst generated from 5 mol % Rh(acac)$(C_2H_4)_2$ and 12.5 mol % of phosphoramidite. [b] Determined by chiral HPLC. [c] The absolute configuration of **5b** was established by comparison of the optical rotation with literature values after deprotection.[33]

Solution-Phase Libraries of Phosphoramidite Ligands in the Development of a Catalyst for the Enantioselective Synthesis of *N*-Protected Diarylmethylamines. Initial arylation experiments were performed with *N*-tosyl-protected *p*-chlorobenzaldimine **4a** (Table 3) and 3 equiv of phenylboronic acid. Solvent variation revealed that 1,4-dioxane, which is generally used as a solvent in the arylation of N-protected benzaldimines,[26,27] could be replaced by the nontoxic acetone. Experiments in acetone, 1,4-dioxane, tetrahydrofurane, methyl *i*-butyl ketone, 2-butanone, ethyl acetate, and dimethyl carbonate at reflux temperature gave similar results for conversion and enantioselectivity.[37] In

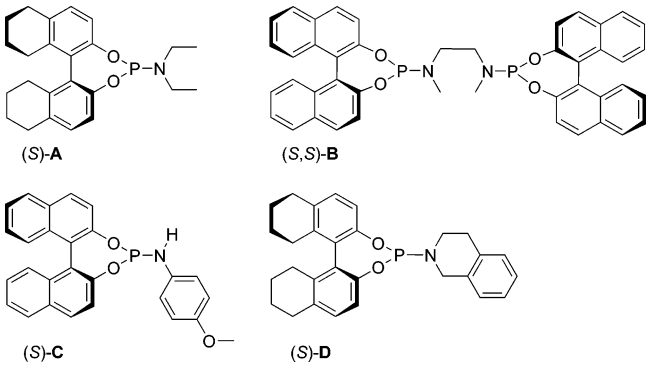


Figure 2. Selected phosphoramidite ligands affording excellent rhodium catalysts for the arylboronic acid addition to enones (A),[42] aldehydes (B),[23a] imines (C),[32] and ketones (D).[43]

contrast to the addition of arylboronic acids to aldehydes, protic solvents (i.e., ethanol and 2-propanol) were found to have a negative effect on the conversion.

To identify the optimum ligand structure for the catalyst, a diverse primary library of 21 phosphoramidites **L1**{*x*} based on (*S*)-BINOL was prepared in a parallel approach as indicated before. The obtained solution-phase library was tested in the addition of phenylboronic acid to **4a**. A fixed amount of the phosphoramidite stock solutions was transferred to 21 corresponding reaction vials, using a liquid handling robot, in an aluminum heating block, followed by an acetone stock solution of the rhodium precursor. After the addition of stock solutions of substrate **4a** (0.1 mmol) and phenylboronic acid (3 equiv) in acetone, the vials were sealed. The aluminum block with the 21 closed vials was heated overnight at reflux temperature. Chiral HPLC analysis of the resulting reaction mixtures showed that ligands based on primary amines gave the highest enantioselectivities (Table 3). Aniline-derived ligand **L1**{*5b*} gave a promising enantioselectivity of 83%.

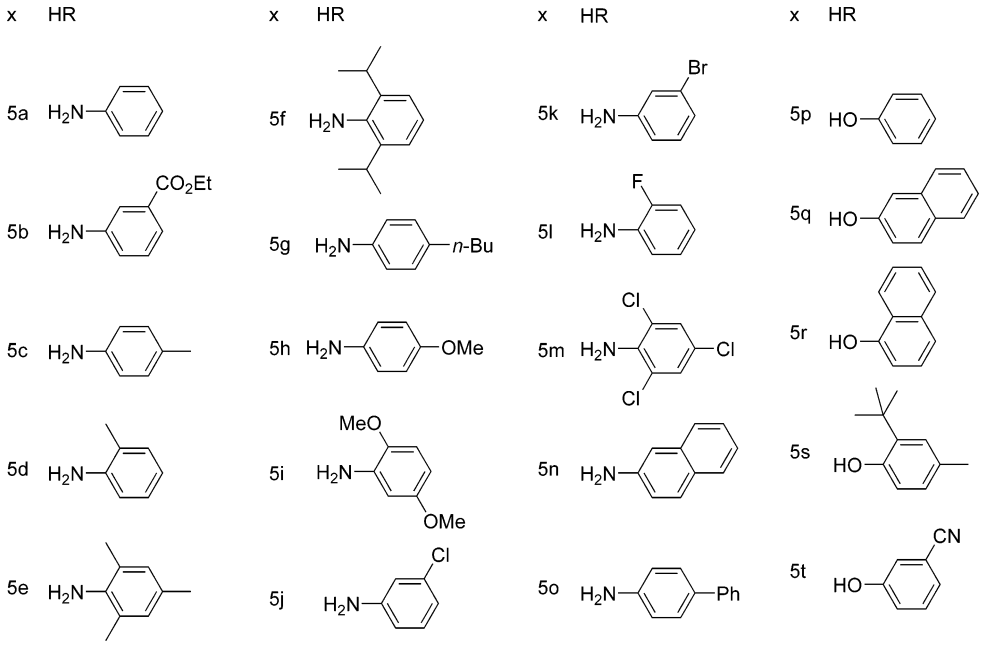
When a representative part of the primary ligand library was screened in the phenylboronic acid addition to *N*,*N*-dimethylsulfamoyl-protected *p*-chlorobenzaldimine **4b**, a significant increase in enantioselectivity was observed with phosphoramidites based on secondary amines (Table 4). Probably, the *N*,*N*-dimethylsulfamoyl protecting group causes a different steric environment around the substrate imine functionality compared to the tosyl group. This seems to be an important factor in the increase of the enantioselectivity when using more bulky phosphoramidites.

A dramatic increase in enantioselectivity in the case of **L1**{*20*} and **L1**{*26*}, the most bulky phosphoramidites in the series, further supports this hypothesis. In the case of phosphoramidites based on primary amines, the introduction of the new protecting group hardly brought about a change in enantioselectivity. However, aniline-based ligands still showed the highest enantioselectivities with values comparable to those found with *N*-tosyl-protected substrate **4a**.

A more focused secondary library of phosphoramidites and phosphites **L2** was prepared from a variety of anilines and phenols with different substitution patterns (Chart 2).

In situ screening of this library on the phenylboronic acid addition to **4b** revealed *p*-anisidine-based ligand **L2**{*5h*} as the ligand showing the highest enantioselectivity in this reaction, although it should be noted that *meta*-halogen-substituted ligands **L2**{*5j*} and **L2**{*5k*} also provided very good results (Table 5). The R enantiomer of ligand **L2**{*5h*} was prepared manually on a preparative scale in a 61% isolated yield. Further optimization of the rhodium-catalyzed addition reaction of phenylboronic acid to **4b** revealed that the enantioselectivity could be improved by lowering the temperature to 40 °C.[32] Furthermore, the minimum amount of phenylboronic acid necessary for the reaction to proceed to full conversion was determined to be as low as 1.3 equiv. With a catalyst generated from 3 mol % $Rh(acac)(C_2H_4)_2$ and 7.5 mol % (*R*)-**L2**{*5h*} the product (*R*)-**5b** was obtained in a 95% yield and a 95% ee. The catalyst loading could be lowered to 1 mol % of catalyst, with only a marginal drop

Chart 2. Anilines and Phenols Used in the Preparation of Secondary Solution-Phase Ligand Library **L2**{*x*}



in selectivity, when the synthesis of (*R*)-**5b** was performed on a gram scale.

Conclusions

A ligand library approach to the development of catalysts for the asymmetric addition of arylboronic acids to aromatic aldehydes and aromatic aldimines has resulted in new rhodium/phosphoramidite catalysts that provide the desired products in good to excellent enantioselectivities and yields. The value of this approach is underscored by the outcome that different substrate classes require different phosphoramidite ligands (Figure 2), an observation that contrasts with the commonly used concept of privileged ligands.

It is shown that an in situ prepared solution-phase phosphoramidite library gives reliable results in terms of enantioselectivity when monodentate ligands are screened. The current methodology is fully implemented in our laboratory in the ligand-discovery process for various new transformations.

Experimental Section

General Remarks. All air- and moisture-sensitive manipulations were carried out under a dry nitrogen atmosphere using standard Schlenk techniques. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 (300 and 75 MHz, respectively) in $CDCl_3$ unless stated otherwise. Mass spectra (HMRS) were recorded on an AEI MS-902. Optical rotations were measured on a Schmidt and Haensch Polartronic MH8. $Rh(acac)(C_2H_4)_2$ was purchased from Strem and used without further purification. All other chemicals were purchased from Acros and were used as received. Flash chromatography was performed using silica gel 60 Å (Merck, 230−400 mesh). Ligand libraries were synthesized using a Zinsser Lissy liquid-handling robot equipped with 4 probes and placed inside a glove box. Whatman PKP 2 mL 96-well filter plates in combination with the UniVac 3 vacuum manifold were used to perform the parallel filtration of the ligand library. Screening of the ligand libraries was performed in a parallel reactor consisting of an aluminum block on a magnetic stirrer/heater containing 32 10 mL vials equipped with magnetic stirring bar, screwcap, and septum. Substrate **4a** was synthesized according to a literature procedure.[38] A procedure for the synthesis of sulfamoyl imine **4b** and isolated ligand **L**{*5h*}, including spectral data, has been reported in ref 31. All other isolated ligands and phosphorochloridite **2** were prepared according to the literature procedure reported in ref 15h. Spectral data for **L1**{*10*}, **L1**{*14*}, **L1**{*15*}, **L1**{*17*}, **L1**{*21*}, **L1**{*24*}, **L1**{*25*}, **L1**{*26*}, and **L1**{*27*} have been reported in ref 39. Spectral data for **L1**{*12*} have been reported in ref 40. Spectral data for **L1**{*16*}, **L1**{*19*}, **L1**{*20*}, **L1**{*22*}, **L1**{*23*}, and **L1**{*24*} have been reported in ref 41. Optimized procedures and spectral data for the synthesis of diarylmethanols with ligand **L1**{*27*} and diarylmethylamines with ligand **L1**{*5h*}, along with a study of the scope of the developed catalysts, have been reported in refs 23a and 32, respectively.

Procedure for the Automated Synthesis of a Solution-Phase Ligand Library. The preparation of ligand libraries was based on a previously reported procedure.[17] Stock solutions were prepared by dissolution of the proper amounts of every reagent necessary for the library synthesis in dry toluene (all by weight). For the phosphorochloridite and the triethylamine, a concentration of 0.5 M was used. In the case of monodentate ligands, 1.0 M stock solutions of the corresponding amines were prepared. In the case of bidentate ligands, 0.5 M stock solutions of the corresponding diamines were prepared. With the liquid handling robot, 100 μL of the phosphorochloridite solution and 100 μL of the triethylamine solution were transferred into the wells of a Whatman PKP filter plate. Next, 50 μL of each of the amine solutions was added to the corresponding well. The microplate was placed on an orbital shaker and gently vortexed for 2 h at room temperature. The microplate was then placed onto the vacuum manifold and filtration was performed upon application of vacuum. The filtrates, that is, solutions of different ligands in dry toluene, were collected and stored in a 96-well polypropylene microplate.

General Procedure for the Automated In Situ Screening of a Solution-Phase Ligand Library. Stock solutions were prepared in the appropriate solvent containing $Rh(acac)(C_2H_4)_2$ at a concentration of 0.05 M and the substrate at a concentration of 0.05 M. With the liquid handling robot, 62.5 μL of the ligand solutions (12.5 μmol for monodentate ligands and 6.25 μmol for bidentate ligands) was transferred from the microplate into vials, equipped with stirring bars. Then, 100 μL of $Rh(acac)(C_2H_4)_2$ (5.0 μmol) and 2 mL of substrate stock solution (0.1 mmol) was added to each of the vials. After the addition of 36.3 mg (0.3 mmol) of phenylboronic acid the vials were capped and transferred to the parallel reactor. The reaction mixtures were left stirring overnight at reflux. After evaporation of the solvent, the obtained solids were analyzed by chiral HPLC to determine the enantiomeric excess.

(4-Chlorophenyl)phenylmethanol (3). Chiralcel AD column with *n*-heptane/2-propanol: 95/5, flow = 1.0 mL min^{-1}. Retention times: 11.3 (R enantiomer) and 12.1 min (S enantiomer).

***N*-[(4-Chlorophenyl)phenylmethyl]-4-methylbenzenesulfonamide (5a).** Chiracel OD-H column with *n*-heptane/2-propanol: 80/20, flow = 1.0 mL min^{-1}. Retention times: 6.2 and 7.5 min.

***N*-(Dimethylsulfamoyl)-*C*-(4-chlorophenyl)-*C*-phenylmethyleneamine (5b).** Chiralcel OD-H column with *n*-heptane/isopropanol: 90/10, flow = 0.5 mL min^{-1}. Retention times: 14.0 and 16.9 min.

Acknowledgment. Financial support was received from DSM Pharmaceutical Products, the Ministry of Economic Affairs, and the chemistry division of The Netherlands Organization for Scientific Research (NWO/CW), administered through the NWO/CW Combichem Program. We thank Mrs. T. D. Tiemersma-Wegman for technical support. Dr. L. Lefort and Dr. A. H. M. de Vries of DSM Pharmaceutical Products are acknowledged for useful discussions.

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CC060161K