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Application of a Supramolecular-Ligand Library for the Automated Search for Catalysts for the Asymmetric Hydrogenation of Industrially Relevant Substrates

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Abstract: A procedure is described for the automated screening and lead optimization of a supramolecular-ligand library for the rhodium-catalyzed asymmetric hydrogenation of five challenging substrates relevant to industry. Each catalyst is (self-) assembled from two urea-functionalized ligands and a transition-metal center through hydrogen-bonding interactions. The modular ligand structure consists of three distinctive fragments: the urea binding motif, the spacer, and the ligand backbone, which carries the phosphorus donor atom. The building blocks for the ligand synthesis are widely available on a commercial basis, thus enabling access to a large number of ligands of high structural diversity. The simple synthetic steps enabled the scale-up of the ligand synthesis to multigram quantities. For the catalyst screening, a library of twelve new chiral ligands was prepared that comprised substantial variation in electronic and steric properties. The automated procedures employed ensured the fast catalyst assembly, screening, and direct acquisition of samples for analysis. It appeared that the most selective catalyst was different for every substrate investigated and that small variations in the building blocks had a major impact on the catalyst performance. For two substrates, a catalyst was found that provided the product with outstanding enantioselectivity. The subsequent automated optimization of these two leads showed that an increase of catalyst loading, dihydrogen pressure, and temperature had a positive effect on the catalyst activity without affecting the catalyst selectivity.

Keywords: asymmetric catalysis · high-throughput screening · hydrogenation · rhodium · supramolecular chemistry

Introduction

In the search for suitable catalysts for the asymmetric synthesis of fine chemicals in industry, time constraints and cost efficiency are the decisive considerations.[1] Despite considerable efforts in academia and industry, these demands still represent a large barrier for the wider application of homogeneous enantioselective catalysis. The current mechanistic knowledge, although far advanced, does not provide sufficient tools to design a catalyst ab initio that will display the required (enantio-) selectivity for a certain envisioned application because small differences in the transition-state energies of the competing pathways (1–2 kcal mol^{-1} similar to the energy required for C–C bond rotation in ethane) already leads to huge selectivity changes.[2] Therefore, subtle variation in ligand structure can cause significant changes in enantioselectivity. The most successful strategy, consequently, comprises the design of modular ligands that are synthetically easily prepared because it enables the preparation of many analogues of a promising ligand type.[3] Besides smart modular design, empirical approaches are often guided by knowledge-based intuition or serendipity. The use of high-throughput experimentation (HTE) and ligand libraries for asymmetric transformations tremendously increases the pace of ligand screening and is therefore highly desirable.[4] Considering the large potential of HTE, its impact in homo-

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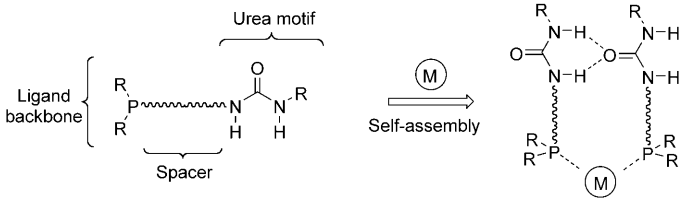
geneous catalysis has been surprisingly modest until recently mainly because the synthetic procedures for chiral ligands are often quite tedious and there is only limited technology available to prepare large catalyst libraries of sufficient size and diversity.[5] This factor is clearly reflected in the scarceness of reports on automated preparations of phosphorus ligands.

The revival of easy-to-synthesize monodentate ligands has provided new opportunities for the application of HTE technology in this field.[6,7] De Vries et al. have shown very elegantly that monodentate phosphoramidites ligands can be prepared in a parallel fashion and subsequently screened in catalysis without difficult purification steps in between.[8] These so called "instant libraries" provide a very efficient tool to prepare and screen a series of 96 catalysts in only two days.[9] This protocol has already resulted in the discovery of a new catalyst that currently is applied on a ton-scale commercial process.[10]

Bidentate ligands represent a different important class of ligand, but automated procedures to make large libraries of this type of ligand are unknown to date.[11] The recent breakthrough of supramolecular bidentate ligands simplifies the preparation of bidentate ligands through the self-assembly of two monodentate ligand building blocks.[12] The bidentate ligands are formed by simply mixing the proper monodentate ligand building blocks with complementary binding motifs, such as hydrogen-bonding,[13] ionic,[14] or metal–ligand interactions.[15] It has been shown that this is a very powerful tool to construct ligand libraries because of the modular nature of the assembling components. We recently reported UREAphos ligands as a new class of supramolecular bidentate ligand that form through urea hydrogen bonding (Scheme 1).[16] These urea-functionalized ligands are made by connecting three building blocks that are amenable for ligand variation, that is, ligand backbone, spacer, and urea motif, thus favoring the development of large and diverse ligand libraries. Two of these ligands form a supramolecular bidentate in the presence of a transition-metal center through self-assembly. An introductory series of six structurally related ligands was explored for rhodium-catalyzed asymmetric hydrogenation and showed high selectivities. These results encouraged us to make use of the potential to enlarge and diversify the number of ligand building blocks and to expand the substrate scope in rhodium-catalyzed asymmetric hydrogenation.

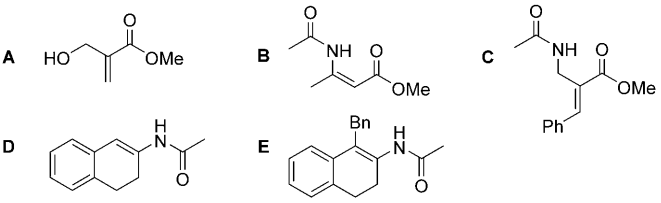


Scheme 1. Self-assembly of the supramolecular catalyst through the hydrogen-bonding interactions of urea. M = metal center.

Herein, we report the development of a library of twelve new structurally diverse UREAphos ligands that were applied as ligands in the rhodium-catalyzed asymmetric hydrogenation of five industrially relevant substrates. Because the easy catalyst-assembly process is potentially a valuable tool for the fast lead discovery in industry, we intended to perform the catalyst screening by means of HTE in an automated environment. Interesting leads from the screening phase were subsequently investigated for optimal reaction conditions in an automated environment. The strategy was accordingly set up in three consecutive stages: 1) preparation of the ligand library, 2) automated catalyst assembly and high-throughput screening, and 3) automated lead optimization.

Results and Discussion

Choice of substrates: The investigated substrates are precursors for the synthesis of high-value compounds of interest for industry. The scope of the substrates is varied notably in the structure and substitution pattern of the prochiral olefin (Scheme 2). The least-substituted substrate methyl 2-(hydroxymethyl)acrylate (**A**; its product is also known as the Roche ester)[17] is used as a building block in the synthesis of the antitumor agents tedanolide and discodermolide.[18] The trisubstituted (unnatural) β-amino acid precursors (*Z*)-methyl 3-acetamidobut-2-enoate (**B**)[19] and (*E*)-methyl 2-(acetamidomethyl)-3-phenylacrylate (**C**)[7j] are interesting building blocks for the synthesis of biologically active β-peptide chains, which are stable to proteolytic degradation.[20] Currently no efficient catalyst is reported to obtain **C** with high enantioselectivity. The asymmetric hydrogenation of the trisubstituted cyclic enamide *N*-(3,4-dihydro-2-naphthalenyl)acetamide (**D**)[15b,21] is interesting for obtaining chiral amines to synthesize many biologically active compounds, such as the melanin-concentrating hormone antagonist as a potential therapeutic agent for obesity.[22] Tetrasubstituted substrates, such as the cyclic enamide *N*-(1-benzyl-3,4-dihydronaphthalen-2-yl)acetamide (**E**) are notoriously hard to hydrogenate with high conversion and enantioselectivity.[23] This compound is used as a building block for the synthesis of β-aminotetralin compounds, which potential TRPV1 an-



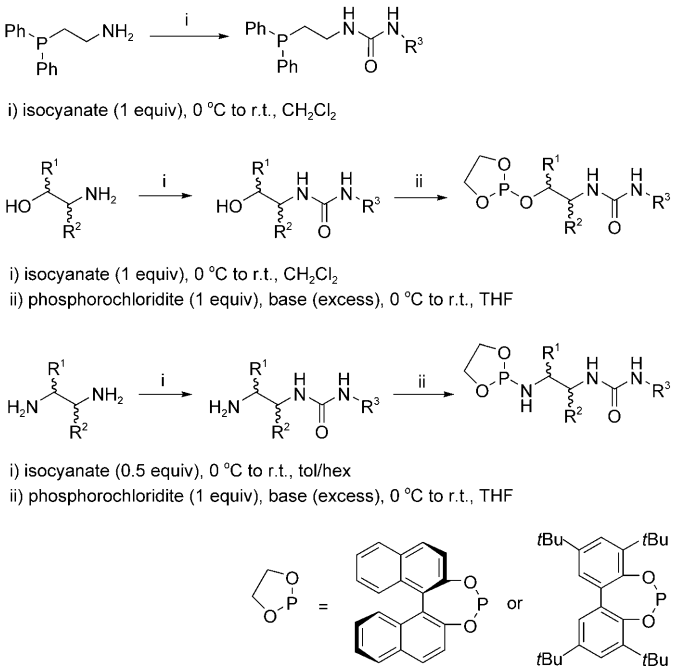
Scheme 2. Substrates **A**–**E**.

tagonists for the treatment of inflammatory pain and other painful conditions in mammals.[24] There is also no efficient catalyst reported to obtain the hydrogenation product of **E** with high enantioselectivity.

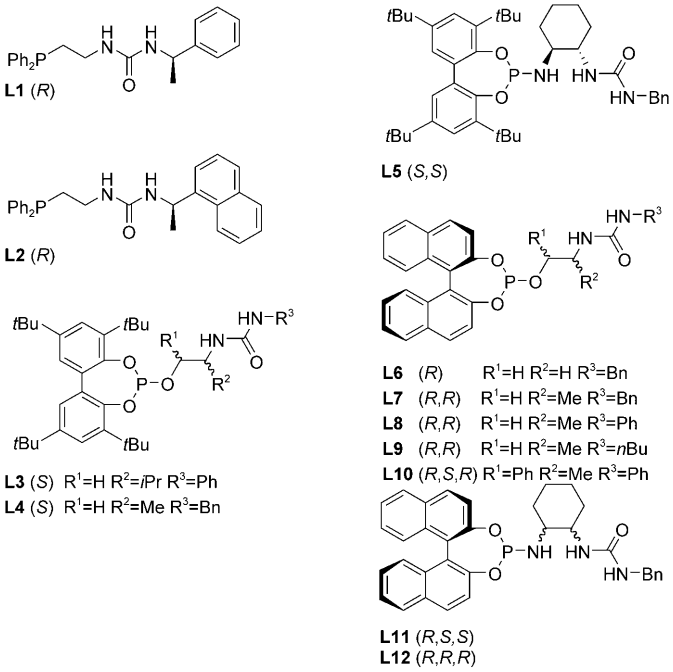
Preparation of the ligand library: Three types of urea-functionalized phosphorus ligands, with varying electronic properties, were prepared: phosphites, phosphoramidites, and phosphanes (Scheme 3). The steric properties were varied by changing the substitutional groups at defined positions in the backbone, spacer, and urea motif. The synthesis of the phosphite ligands starts with the coupling of an isocyanate with an amino alcohol followed by a condensation reaction with a phosphorochloridite. The synthesis of phosphoramidite ligands is virtually analogous to the synthesis of phosphites. In the first step, the urea amine is formed by coupling an isocyanate with a twofold excess of the diamine followed by a condensation reaction with a phosphorochloridite. The synthesis of phosphane ligands is accomplished by a single reaction of an amino phosphane with an isocyanate. According to these synthetic procedures, a library of twelve new UREAphos ligands was prepared manually by using almost exclusively commercially available building blocks (Scheme 4). All the ligands were fully characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopic and high-resolution mass-spectrometric analysis.

The two phosphanes **L1** and **L2** were synthesized from 2-(diphenylphosphano)ethanamine coupled to a chiral isocyanate and are the only ligands with stereogenic elements exclusively at the urea motif. Phosphites **L3** and **L4** and phosphoramidite **L5** all contain a flexible pro-atropoisomeric (tropos) backbone, which is amenable for the transfer of chirality from the stereogenic groups in the spacer.[25] Phosphite **L3** has a relatively bulky stereogenic isopropyl group at the R^2 position of the spacer, whereas phosphite **L4** contains a less sterically demanding stereogenic methyl group at the same position. The spacer of **L5** is based on (1*S*,2*S*)-cyclohexane-1,2-diamine. Phosphites **L6**–**L10** all have the same (*R*)-BINOL-derived (BINOL = 1,1′-bi-2-naphthol) backbone and vary only in the spacer and urea motif. Ligand **L6** contains a benzyl urea motif and no substituents at all in the spacer. Ligands **L7**–**L9** contain only an additional stereogenic methyl group at the R^2 position of the spacer and vary by the benzyl, phenyl, and *n*-butyl urea motifs, respectively. Ligand **L10** carries a stereogenic phenyl group at the R^1 position close to the phosphorus donor atom and a stereogenic methyl group at the R^2 position in combination with a phenyl urea motif. The phosphoramidites **L11** and **L12** are diastereomers, which consist of a cyclohexane-1,2-diamine spacer (1*S*,2*S* and 1*R*,2*R* isomers for **L11** and **L12**, respectively) coupled to a benzylisocyanate and a *R*-BINOL-derived backbone.

A multigram-scale (83 g) batch of phosphite **L8** was prepared to demonstrate the possibility of scaling up the ligand synthesis. Instead of an excess of triethylamine as the base to trap HCl as a salt, a solid Amberlyst base was used, which is easily filtered off after completion of the reaction.[26] Remaining HCl salts present in the product would have a deleterious effect on the activity in the rhodium-catalyzed hydrogenation, and therefore need to be removed.[8] For automated synthesis and multigram-scale synthesis, the solid-base method is suitable because of the simple separa-



Scheme 3. Synthesis of different types of UREAphos ligands. hex = hexane, tol = toluene.



Scheme 4. UREAphos ligands **L1**–**L12**.

tion step involved. This approach ensures that all the employed synthetic (i.e., coupling of amine and isocyanate groups and condensation of the PCl and alcohol moieties) and purification steps (i.e., filtration and recrystallization) are viable reaction paths in an industrial environment.

Complex and dilution studies: Complex and dilution studies were performed with phosphane ligand **L2** as an exemplary ligand of the library to investigate the coordination behavior and the nature of the hydrogen bonding in the supramolecular assembly. The coordination study was carried out with $[Rh(nbd)_2]BF_4$ (nbd = 2,5-norbornadiene) as the metal precursor and two equivalents of **L2**. The $^{31}P\{^1H\}$ NMR spectrum showed a doublet that indicated the formation of a complex with two equal ligands with a coupling constant

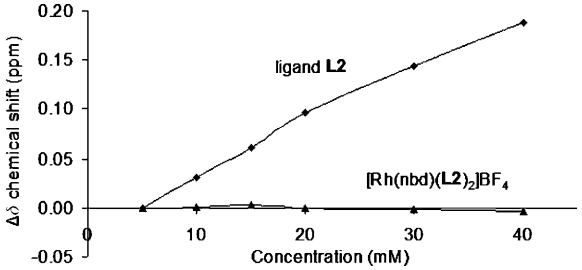


Figure 1. Dilution study of ligand **L2** and $[Rh(nbd)(\mathbf{L2})_2]BF_4$.

($J_{Rh-P} = 152$ Hz) that is typical for a *cis* geometry (Figure 1).[27] The ^1H NMR spectrum indicated that only one nbd unit remained coordinated. The general structure of $[Rh(nbd)(\mathbf{L2})_2]BF_4$ was confirmed by using HRMS (calcd for $C_{61}H_{62}O_2N_4P_2Rh$: 1047.3403; found: 1047.3395).

A dilution study of ligand **L2** and complex $[Rh(nbd)(\mathbf{L2})_2]BF_4$ was performed and the signal of one of the urea protons (CH_2–N*H*; the position of which was determined by COSY ^1H NMR) was monitored by ^1H NMR spectroscopic analysis in the concentration range 5–40 mM

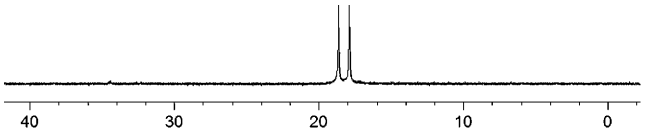


Figure 2. $^{31}P\{^1H\}$ NMR spectrum of $[Rh(nbd)(\mathbf{L2})_2]BF_4$.

(Figure 2). The urea proton signal of the ligand shows a strong dependency on the concentration because of the formation of intermolecular hydrogen bonds.[28] The same urea proton signal in the complex $[Rh(nbd)(\mathbf{L2})_2]BF_4$ was shifted downfield with respect to **L2** by more than $\Delta\delta = 1$ ppm and showed no dependency on concentration because of intramolecular hydrogen bonding. These results support the formation of the supramolecular bidentate species through urea hydrogen bonding. Furthermore, these results are in accordance with a complex and dilution study performed with a structurally similar phosphite ligand to **L8**, which provided comparable results.[16b]

Automated catalyst assembly and high-throughput screening: An automated sequence was programmed in an Accelerator SLT workstation of Chemspeed Technologies to prepare the catalyst reaction mixtures and perform the subsequent catalyst screening (60 experiments in total).[29] Samples of the product mixtures for GC analysis were prepared automatically directly after completion of the sequence. The results of the screening experiments are presented in Table 1.

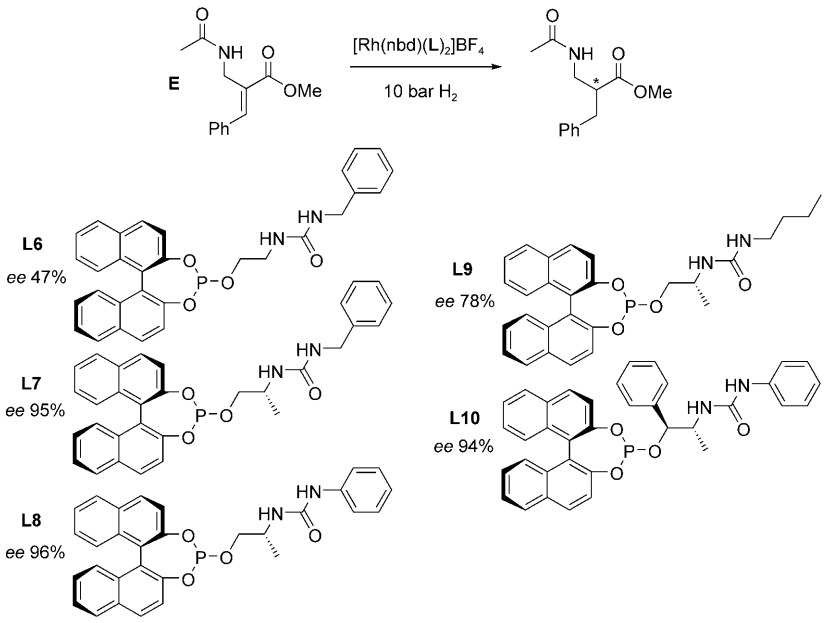
In general, these results show that the conversion and enantiomeric excess (*ee*) are strongly influenced by the ligand type and changes in the ligand structure, which is also evidenced by the fact that for every substrate a different catalyst performed best in terms of selectivity. Interestingly, for defined cases a correlation was found between the catalyst performance and variations in the ligand structure. These variations expressed by the ligand backbone, spacer (R^1 and R^2 position), and urea moiety (R^3 position) allowed us to

Table 1. Results of the high-throughput screening of substrates **A**–**E** with ligands **L1**–**L12**.[a]

Substrate	**A**		**B**		**C**		**D**		**E**	
Ligand	Conversion [%]	*ee*[b] [%]	Conversion [%]	*ee*[b] [%]	Conversion [%]	*ee*[b] [%]	Conversion [%]	*ee*[b] [%]	Conversion [%]	*ee*[b,c] [%]
L1	49	21 (+)	13	–	–	–	70	53 (+)	6.4	26 (+)
L2	14	–	–	–	–	–	36	14 (+)	25	34 (+)
L3	100	4.5 (+)	36	64 (+)	–	–	34	23 (−)	3.0	19 (−)
L4	100	30 (+)	100	–	–	–	18	53 (−)	2.0	44 (−)
L5	45	13 (+)	–	–	–	–	–	–	–	–
L6	80	–	6.8	27 (−)	34	47 (+)	18	19 (+)	8.6	20 (+)
L7	100	–	21	15 (−)	16	95 (+)	36	24 (+)	4.6	71 (+)
L8	88	14 (+)	8.7	45 (−)	23	96 (+)	20	24 (+)	3.0	71 (+)
L9	100	–	29	31 (−)	18	78 (+)	2	26 (+)	3.8	72 (+)
L10	100	33 (+)	33	38 (−)	33	94 (+)	14	66 (+)	5.2	69 (+)
L11	66	54 (−)	–	–	1.6	62 (+)	3.2	15 (+)	5.4	13 (+)
L12	54	17 (−)	6.5	76 (−)	–	–	29	32 (−)	–	–

[a] Reaction conditions: [Rh] = 1 mM $[Rh(nbd)_2]BF_4$, [L] = 2.2 × [Rh], [S] = 50 × [Rh], reaction time = 12 h, temperature = RT, pressure = 10 bar H_2, solvent = CH_2Cl_2. [b] The signs are reported to emphasize changes in the absolute chirality of the product as measured by GC and HPLC; however, the signs do not reflect a measured optical rotation. [c] Only the *cis*-hydrogenated product was observed.

emphasize relevant structural elements to obtain high selectivity for a specific substrate. Phosphoramidite **L11** serves as an illustrative example of applied changes in the ligand structure as an *ee* value of 54% was obtained for substrate **A**, whereas the diasteromeric phosphoramidite **L12** led to a low *ee* value of 17%. Other ligands performed rather poorly for this substrate and only low-to-modest *ee* values were obtained (<33%). In the case of substrate **B**, again the diastereomeric phosphoramidites **L11** and **L12** differed distinctively. The highest *ee* value was accomplished with **L12** (76%), whereas with **L11** the complex was completely inactive. Interestingly, also the tropos-based phosphite **L3** led to an *ee* value of 64%, whereas with the analogous tropos-based phosphite **L4** a racemic product was obtained. The other ligands of the library performed poorly with *ee* values lower than 45%. In the case of **C**, the phosphites **L6–L10** were the only ligand type that provided active catalysts (Scheme 5). The *ee* values obtained with **L6** and **L9** (47 and 78%, respectively) were only moderate but very high *ee* values were obtained with **L7**, **L8**, and **L10** (95, 96, and 94%, respectively), which are currently the highest reported *ee* values for this substrate.[7j,30] These ligands have the BINOL-derived backbone, the stereogenic methyl group at the R^2 position of the spacer, and a phenyl or benzyl urea motif in common. Ligands that lack these substitution patterns, such as **L6** and **L9**, were less successful. In the case of substrate **D**, all the ligand types provided active catalysts. Remarkably, phosphane **L1** which only has a stereogenic element at the urea moiety reached an *ee* value of 53%, thus also showing that variation in the urea motif can be effective in specific cases. The best result was obtained with BINOL-derived phosphite **L10** (66% *ee*, 14% conversion). Substitution at the R^1 position of the spacer of this phosphite discriminates this ligand from the other BINOL-derived phosphites. Under the conditions applied, the conversions remained low (<10%) for the hydrogenation of tetrasubstituted substrate **E**. The BINOL-derived phosphites **L6–L10** were the most selective ligands with a *ee* value of 72% for **L9**, which is among the highest reported values for this substrate.[23,31] Only **L6** performed relatively poorly (20% *ee*), which indicates that substitution with a stereogenic methyl group at the R^2 position of the spacer is an important structural variation to obtain high enantioselectivity for this substrate.



Scheme 5. Hydrogenation of **E** with phosphites **L6–L10**.

Automated lead optimization: The high-throughput screening provided interesting leads in terms of *ee* values for substrates **C** and **E** (96% with **L8** and 72% with **L9**, respectively); however, the conversion of both substrates (23 and 3.0% for **C** and **E**, respectively) was rather low under the conditions applied. To investigate if the activity of the catalysts could be improved, the reaction conditions were optimized using an automated AMTEC SPR16 robot, which is suited to the application of different reaction conditions in each individual reactor.[32] The reaction conditions varied were temperature, dihydrogen pressure, and, for **E**, the rhodium precursor concentration.

The obtained results for the lead optimization of **C** are presented in Table 2. The optimization experiments showed that within the span of the investigation an increase in temperature and pressure caused an enhancement in the catalyst activity and, therefore, higher conversions. Fortunately, in all cases this enhancement was accompanied by the retention of the catalyst selectivity, which becomes evident by comparing the *ee* value of Entries 1 and 6 (95% *ee* at 10 bar, 25°C versus 96% *ee* at 30 bar, 45°C, respectively; Table 2). Fur-

Table 2. Lead optimization of substrate **C**.[a]

Entry	P_{H_2} [bar]	T [°C]	Conversion [%]	*ee* [%]
1	10	25	29	95
2	10	35	45	97
3	10	45	61	97
4	30	25	45	93
5	30	35	64	95
6	30	45	84	96

[a] Reaction conditions: [Rh] = 3.75 mM $[Rh(nbd)_2]BF_4$, [**L8**] = 2.2 × [Rh], [S] = 100 × [Rh], reaction time = 4–5 h, solvent = CH_2Cl_2.

thermore, the conversion for these entries increased from 29 to 84%, respectively.

The lead optimization for **E** was carried out using **L8** (Table 3). Interestingly, the optimization experiments resulted in even higher *ee* values (82–87%) in the lead-optimization experiments, which is explained by the use of more accurate procedures because the reactions carried out by the AMTEC robot were performed on a larger scale. Furthermore, the same retention in catalyst selectivity on changing the reaction conditions was observed for substrate **E**. The *ee* values remained almost constant (compare Entries 1 and 8 in Table 3: 87% *ee* at 10 bar, 25°C, 2.25 mM versus 83% *ee* at 40 bar, 40°C, 3.75 mM, respectively). Because this tetrasubstituted cyclic substrate has a very hindered double bond, it is hydrogenated at a relatively slow rate. However, the conversion could be optimized from 5.6 to 84% and the increase in temperature, pressure, and the additional catalyst loading all had a positive effect on the catalyst activity.

Table 3. Lead optimization of substrate **E**.[a]

Entry	P_{H_2} [bar]	T [°C]	[Rh] [mM]	Conversion [%]	*ee* [%]
1	10	25	2.25	5.6	87
2	10	40	2.25	26	85
3	10	25	3.75	15	86
4	10	40	3.75	42	86
5	40	25	2.25	28	83
6	40	40	2.25	62	82
7	40	25	3.75	45	83
8	40	40	3.75	84	83

[a] Reaction conditions: [**L8**] = 2.2 × [Rh], [S] = 50 × [Rh], reaction time = 28 h, solvent = CH_2Cl_2.

Conclusions

Herein, the preparation of a library of twelve new chiral urea-functionalized ligands that form supramolecular bidentate ligands in the presence of a rhodium catalyst precursor was presented. Although the library is small at this stage, the modular buildup of these ligands from very diverse, commercially available, building blocks enables access to large ligand libraries or rapid optimization of a lead found during screening experiments. In addition, relatively easy synthetic steps have been employed, thus allowing the facile scale-up of the ligands to multigram-scale synthesis, which is demonstrated by the preparation of 83 g of one of the ligands in about one week.

To demonstrate the ability of these ligands to induce selectivity, they were applied in the asymmetric rhodium-catalyzed hydrogenation of five industrially relevant substrates by using automated procedures for high-throughput screening and lead optimization. The screening experiments demonstrated that variation of the electronic and structural properties of the ligands through small changes applied to the urea motif, spacer, and ligand backbone had strong effects on catalyst selectivity. Unrivaled excellent enantioselectivities were obtained for two inherently difficult substrates: 96 and 87% for substrates **C** and **E**, respectively. These results support the significance of large and diverse catalyst libraries for lead discovery. Optimization of the reaction conditions for two successful catalysts showed that catalyst activity is easily improved by varying temperature, pressure, and catalyst loading. These results demonstrate the powerful combination of the application of supramolecular ligands, based on easily accessible ligand building blocks, and automated high-throughput screening of their catalysts, thus leading to new catalyst solutions for industrially relevant substrates.

Experimental Section

General procedures and materials: Unless stated otherwise, the reactions were carried out in an inert atmosphere of nitrogen or argon with standard Schlenk techniques. THF was distilled from sodium benzophenone ketyl, dichloromethane from CaH_2, and toluene from sodium under nitrogen. NMR spectra were measured on a Varian Mercury (^{1}H: 300 MHz; ^{31}P{^{1}H}: 121.5 MHz; ^{13}C{^{1}H}: 75.5 MHz) or a Varian Inova spectrometer (^{1}H: 500 MHz; ^{31}P{^{1}H}: 202.3 MHz; ^{13}C{^{1}H}: 125.7 MHz) at room temperature unless stated otherwise. Chemical shifts are reported in ppm and are given relative to trimethylsilane (TMS; ^{1}H and ^{13}C{^{1}H}) or H_3PO_4 (^{31}P{^{1}H}) as an external standard. High-resolution mass spectra were recorded at the Department of Mass Spectrometry at the University of Amsterdam using FAB$^+$ ionization on a JEOL JMS SX/SX102A four-sector mass spectrometer with 3-nitrobenzyl alcohol as the matrix. With exception of the compounds given below, all the reagents were purchased from commercial suppliers and used without further purification. Triethylamine was distilled from CaH_2 under nitrogen. The following ligand precursor compounds were synthesized according to reported procedures: phosphorochloridite of (*R*)-2,2′-bisnaphthol,[33] 3,3′,5,5′-tetra-*tert*-butyl-2,2′-bisphenol,[34] and phosphorochloridite of 3,3′,5,5′-tetra-*tert*-butyl-2,2′-dihydroxybisphenol.[35] Substrates **A**,[36] **B**,[19b] **C**,[7j] **D**,[21c] and **E**[23] were also synthesized according to reported procedures.

General procedure for the preparation of urea alcohols: A solution of isocyanate (5 mmol, 1 equiv) in dichloromethane (10 mL) was added dropwise to a vigorously stirred solution of the amino alcohol (5 mmol, 1 equiv) in dichloromethane (20 mL) kept at 0°C. The reaction mixture was allowed to warm to room temperature and was left stirring for 1 h. The formed precipitate was filtered off and washed twice with hexanes. The remaining solvents were evaporated in vacuo to obtain the product almost quantitatively.

General procedure for the preparation of urea amines: A solution of isocyanate (5 mmol, 1 equiv) in toluene/hexanes (10 mL, 1:1) was added dropwise to a vigorously stirred solution of diamine (10 mmol, 2 equiv) in toluene/hexanes (20 mL, 1:1) kept at 0°C. The reaction mixture was allowed to warm to room temperature and was left stirring for 1 h. The formed precipitate was filtered off and washed twice with hexanes. The remaining solvents were evaporated in vacuo to obtain the product. The starting material diamine was recovered from the filtrate.

General procedure for the preparation of urea phosphites and urea phosphoramidites: A solution of phosphorochloridite (1 mmol, 1 equiv) dissolved in THF (10 mL) was added dropwise to a vigorously stirred solution of the urea alcohol or urea amine (1 mmol, 1 equiv; dried by the coevaporation with toluene (3×)) and an excess of triethylamine in THF (20 mL) kept at 0°C. The turbid reaction mixture was subsequently warmed to room temperature and left stirring for 12 h. After filtration over a small layer of neutral alumina oxide and evaporation of solvents, the product was obtained almost quantitatively. If necessary, the product was purified by column chromatography with dichloromethane/ethyl acetate (4:1) as the eluent. After evaporation of the solvents in vacuo, the last traces of ethyl acetate were removed by coevaporation with toluene.

General procedure for the preparation of urea phosphanes: A solution of isocyanate (5 mmol, 1 equiv) in dichloromethane was added dropwise to a vigorously stirred solution of amino phosphane (5 mmol, 1 equiv) in dichloromethane (20 mL) kept at 0°C. The reaction mixture was allowed to warm to room temperature and was left stirring for 2 h. After evaporation of the solvents in vacuo, the product was obtained almost quantitatively.

Multigram synthesis of L8: Amberlyst A-21 (430 g) and urea alcohol **U4** (0.505 mol, 97.86 g, 1 equiv) were dried by coevaporation with toluene (3×) in a 3-L flask, and THF (500 mL) was added as a solvent. The reaction mixture was cooled in an ice bath and a solution of phosphorochloridite of (*R*)-2,2′-bisnaphthol (0.505 mol, 1 equiv) in toluene was added slowly. The reaction mixture was stirred overnight at 45°C. The reaction mixture was filtered and the Amberlyst A-21 washed with THF. The solvents were evaporated in vacuo to give the crude product. The product was purified by recrystallization from dichloromethane/petroleum ether to give a white powder (33%, 0.16 mol, 83 g).

General procedure for complex and dilution studies: The complex study was carried out on a sample (0.5 mL) in $CDCl_3$ (20 mM) by mixing one equivalent of the catalyst precursor $[Rh(nbd)_2]BF_4$ (nbd = 2,5-norbornadiene) with two equivalents of **L2**. The ^1H NMR dilution experiments were carried out by preparing a sample (0.5 mL) at a known concentration: 5, 10, 15, 20, 30, and 40 mM in $CDCl_3$ for **L2** and for $[Rh(nbd)(\mathbf{L2})_2]BF_4$. The position of the solvent signal was used as a reference for the urea NH signal.

General procedure for catalyst-screening experiments: The high-throughput screening experiments were carried out in a Chemspeed Accelerator SLT workstation. All the experiments were conducted in an inert atmosphere. For a typical screening experiment (hydrogenation), stock solutions of the ligands (3.85 mM), catalyst precursor $[Rh(nbd)_2](BF_4)$ (3.5 mM), and substrate (175 mM) in dry dichloromethane were prepared. The ligands (2×1.0 mL) and catalyst precursor (1.0 mL) were mixed in the reactor. The substrate (1.0 mL) was added after vortex mixing for 5 min. This procedure resulted in catalyst and substrate concentrations of 1.0 and 50 mM, respectively, in the reactor. The hydrogenation was carried out at dihydrogen pressure of 10 bar at room temperature for 12 h. The hydrogenation products of substrates **A**–**D** were analyzed with an Interscience Trace GC Ultra (FID detector) equipped with a CP Chiralsil DexCB column. The hydrogenation products of substrate **E** were analyzed on a Shimadzu 10 A HPLC chromatograph equipped with a UV detector (column: Chiralpak AD; eluent: *n*-hexane/isopropyl alcohol (90:10); flow rate: 0.6 mL min^{-1}).

General procedure for lead-optimization experiments: The optimization experiments were carried out in the AMTEC SPR16 slurry-phase reactor and consisted of 16 parallel reactors equipped with temperature and pressure sensors and a mass-flow controller. The apparatus is suited for monitoring gas-uptake profiles during the catalytic reactions for each reactor simultaneously. Four autoclaves were heated to 110°C and flushed with argon (22 bar) five times. Next, the reactors were cooled to 25°C and flushed again with argon (22 bar) five times. The autoclaves were charged with the appropriate amount of catalyst precursor $[Rh(nbd)_2]BF_4$ ligand and substrate in dichloromethane (8.0 mL) under argon. The reactors were pressurized with dihydrogen and the pressure was kept constant during the whole reaction. The reaction mixtures were stirred at the appropriate reaction temperature and the hydrogen uptake was monitored and recorded for every reactor during catalysis. After catalysis, the reactors were cooled down to room temperature and the pressure was reduced to 2.0 bar and samples (0.2 mL) were taken.[37]

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