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Rapid Identification of a Scalable Catalyst for the Asymmetric Hydrogenation of a Sterically Demanding Aryl Enamide

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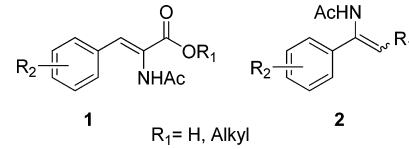
Abstract:

High throughput screening was used to find a cost-effective and scalable catalyst for the asymmetric hydrogenation of a sterically demanding enamide as an intermediate towards a new potent melanocortin receptor agonist useful in the treatment of obesity. Lessons drawn from the testing of a first library of 96 chiral monodentate phosphoramidites led to the design of a second focused library of 16 chiral ligands, allowing the discovery of a new efficient catalyst. This catalyst was based on rhodium and a bulky monodentate phosphite ligand. The catalyst was scaled up and used in the kilogram production of the desired bulky chiral amide.

Introduction

Since the initial success of Knowles with L-DOPA,[1] the Rh-catalyzed asymmetric hydrogenation of *N*-acylated α-dehydro amino acids or esters (Scheme 1, **1**) has received a lot of attention from the scientific community, both academic and industrial.[2] Substrates lacking the acid or ester function, i.e. simple aryl enamides (Scheme 1, **2**), are useful precursors of chiral amides that can be further converted to chiral amines.[3] Although aryl enamides appeared to be more demanding than the corresponding enamide acids or esters, numerous homogeneous catalysts have been developed for their hydrogenation with high enantiomeric excess.[2b,4] The presence of an ortho substituent R_2 (Scheme 1, **2**) on the aromatic ring of the enamide, even as small as Br, can have a detrimental effect on the enantiomeric excess,[5] although consecutive studies reported active and enantioselective catalysts for a limited set of aryl enamides with relatively small ortho substituents (methyl, halides, methoxy).[6]

Scheme 1. **Prochiral substrates for asymmetric hydrogenation**



The aryl enamide we needed to hydrogenate, as part of our customer manufacturing operations, was endowed with a very bulky ortho substituent, i.e. an *N*-Boc piperidyl group (Scheme 2, **3**). The hydrogenation product of this molecule (Scheme 2, **4**) is an intermediate for the preparation of **5**, a potent melanocortin receptor agonist discovered by Merck, and potentially useful in the treatment of obesity.[7] The Merck scientists identified [(*S,S*)-Me-BPE-Rh(COD)]BF_4 (Me-BPE = (−)-1,2-Bis((2S,5S)-2,5-dimethylphospholano)ethane) as an efficient hydrogenation catalyst.[8] Full conversion and an enantiomeric excess of 87−90% were obtained at *S/C* = 500, provided the bulky aryl enamide was washed twice with $NaHCO_3$ solution, and recrystallized prior to the asymmetric hydrogenation.[9]

Chiral monodentate ligands, such as phosphoramidites derived from Binol,[10] are in general an order of magnitude cheaper than chiral bisphosphines, and have shown to be capable of hydrogenating aryl enamides successfully.[11] Moreover, to deal with the severe time constraints imposed on process

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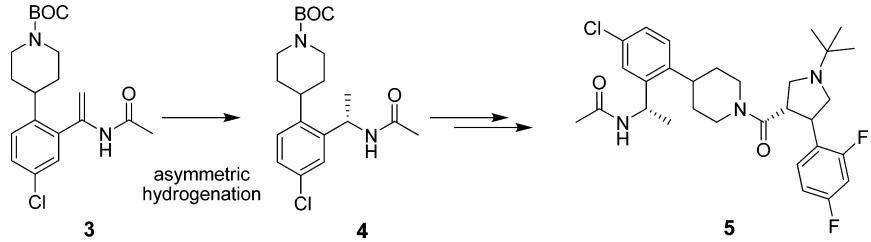
Scheme 2. **Asymmetric hydrogenation of bulky enamide 3 en route to the drug candidate 5**



development in the pharma industry, we have implemented a high throughput set up for the rapid synthesis of a library of 96 chiral phosphoramidite ligands (and other monodentate ligands such as phosphites). This library can be tested in parallel in a custom-made hydrogenation reactor[12] and the entire screening of the 96 ligands is usually completed in less than 2 days.[13] This high throughput experimentation (HTE) setup was a key success factor in the discovery of a new cheap catalyst for the hydrogenation of a dehydrocinnamic acid derivative, an intermediate for the renin inhibitor aliskiren.[14]

In this report, we present the application of this high throughput screening protocol to bulky enamide **3** leading to the discovery of a cost-effective hydrogenation catalyst used for kg production of **4**.

Results and Discussion

Screening for a Phosphoramidite Based Asymmetric Hydrogenation Catalyst. The first rhodium/phosphoramidite-catalyzed hydrogenation experiments were performed in the Endeavor reactor (8 parallel vessels, 0.5 mmol scale in 5 mL of solvent)[15] and were aimed at finding a standard set of experimental conditions to be used in the parallel screening. These initial trials indicated that alcohols (MeOH, EtOH, *i*-PrOH) were better solvents than toluene, EtOAc, MTBE and DCM. A sufficient amount of product (>25% conversion) was obtained within 3 h using 25 bar of H_2 at room temperature to allow measurement of the enantiomeric excess (substrate to catalyst ratio of 50).

Next, a library of 96 phosphoramidite ligands was prepared following our high throughput protocol previously described.[13] The 96 ligands are synthesized in parallel by reaction between a chlorophosphite and an amine. The reaction mixtures are filtered in parallel leading to stock solutions of the ligands that can be combined with $Rh(COD)_2BF_4$ to generate the catalyst. The library was composed of 64 (*R*)-Binol-based ligands (column 1−8), 16 (*R*)-octahydro-Binol-based ligands (Column 9−10) and 16 (*R*)-3,3′-dimethyl -Binol-based ligands (Column 11−12). The 64 amines used in combination with Binol and the 16 amines used in combination with both the octahydro- and dimethyl-Binol are shown in Figure 1.

As can be seen in Figure 1, the amines used are very diverse structurally and electronically. About equal numbers of primary and secondary amines were used. Of these, 11 amines were used in their enantiomerically pure form. Several amines containing an extra coordinating group such as a thioether (**H2**), an amine (**A8** or **B7**), an ether or an acetal (**B8, G7 or H7**) were also included, as well as an amide **(A4),** hydrazines **(D8** and **E8**), and a crown-ether (**D7**).

The 96 phosphoramidites were reacted with 1/2 equivalent of $Rh(COD)_2BF_4$ in DCM for 15 min to allow formation of the catalysts, $Rh(COD)L_2BF_4$ (L=phosphoramidite ligand) and the set of the 96 catalysts was tested in parallel in the asymmetric hydrogenation of **3**. Results are given in Figure 2, following the layout for the ligands as described in Figure 1.

Among the 64 phosphoramidites based on Binol, the conversion varied from 0 to 72% for the ligand based on *t*-$BuNH_2$, **D4**, which also induced quite a good ee relative to the whole library, −47%. Among these 64 ligands, several other ligands based on bulky primary amines with α-branching stood out both in terms of activity and/or enantioselectivity: *i*-$PrNH_2$ (**F4**, 51% conv., −52% ee); *rac*-2-*neo*-pentyl-NH_2 (**A5**, 38% conv., −51% ee); α-(c)-hexyl-ethyl-NH_2 (**G6**, 21% conv., −46% ee and **H6,** 30% conv., −48% ee). The best ee for this set of ligands was also obtained with a rather bulky primary amine containing a morpholine group (**F7**, 29% conv., −59% ee). As a result of the rather large number of ligands tested, one can see a trend emerging: Although the substrate is itself bulky, it seems like a bulky amino part based on primary amines may be needed for high ee and activity. Looking at the results obtained with the ligands based on octahydro-Binol, primary amine based ligands (Column 10) appeared again better than those with secondary amines (Column 9). The highest conversion among these 16 ligands was obtained using the ligand based on *n*-dodecyl amine (**D10**, 45% conv., −45% ee), but the one based on *i*-$PrNH_2$ also induced a relatively good ee (**B10**, 26% conv., −44% ee), confirming the previous observation with the set of ligands based on Binol.

The most interesting results, however, were obtained with ligands based on 3,3′-dimethyl-Binol and primary amines (column 12) with again a ligand based on an α-branched amine resulting in the most active catalyst and the highest enantioselection (**B12**, *i*-$PrNH_2$, 95% conv., 78% ee). Quite surprisingly,

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(15) http://www.biotage.com/DynPage.aspx?id=23682.

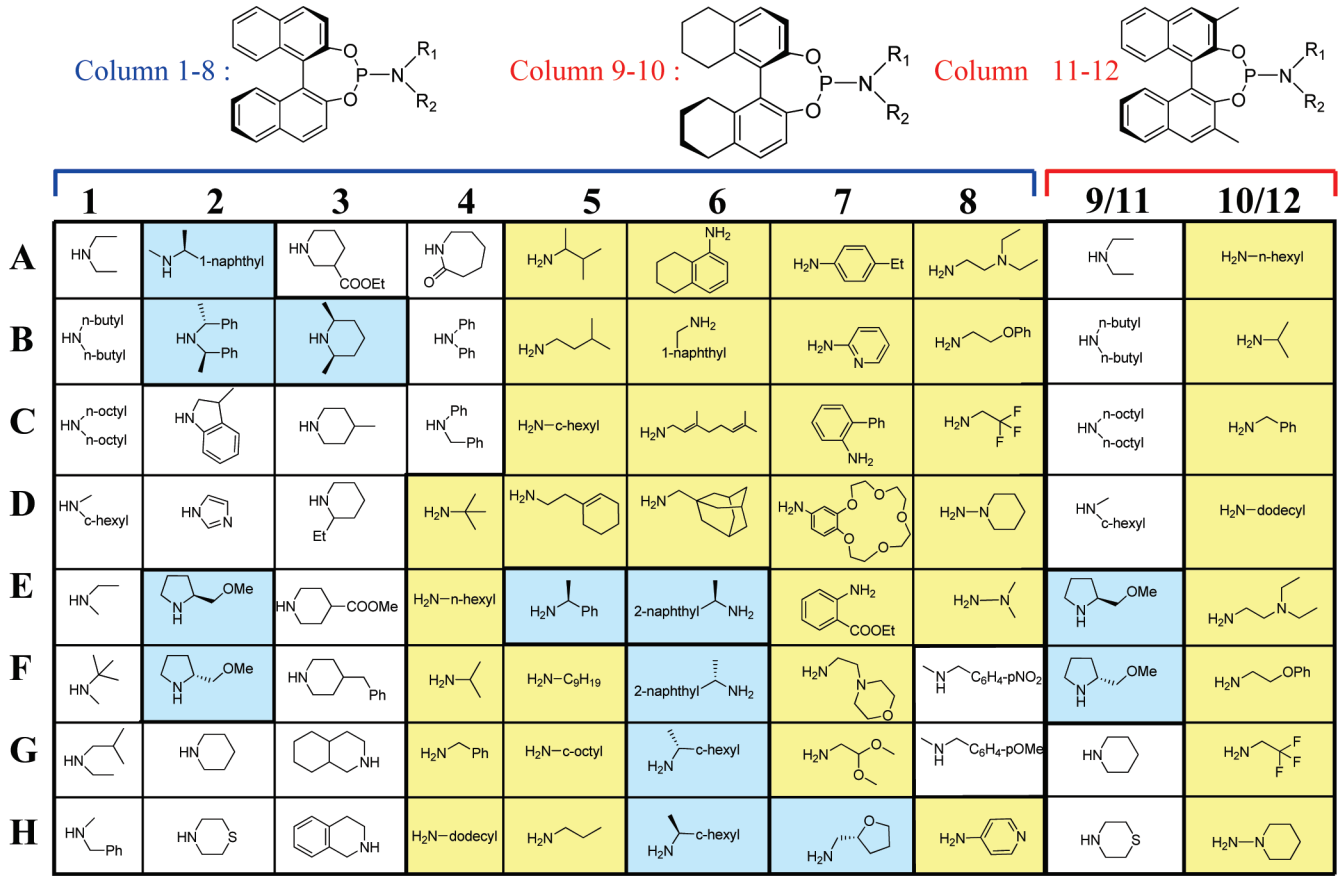


Figure 1. **Set of amines (yellow = 1[ary] amine, white = 2[ary] amine, blue = enantiomerically pure) used to prepare the first library of 96 phosphoramidite ligands.**

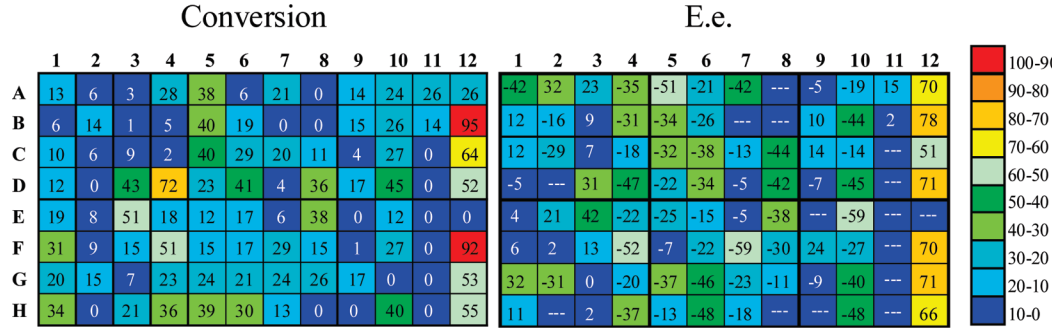


Figure 2. **Results of the screening of the library of the 96 phosphoramidite ligands (Reaction conditions: Rh(COD)L_2BF_4, 25 °C, 25 bar H_2, [3] = 0.073 M in dry EtOH, 3/Rh = 50 mol/mol, reaction time = 3 h).**

catalysts based on the ligands derived from 3,3′-dimethyl-Binol and secondary amines (column 11) hardly showed any activity.

Interestingly, although in all cases the diol has the (*R*)-configuration, ligands based on 3,3′-dimethyl-Binol led predominantly to formation of the desired (*S*)-enantiomer of the product, while the ligands based on Binol and octahydro-Binol led to the (*R*)-product. This could indicate a different coordination behaviour or a different active catalyst configuration when ligands derived from 3,3′-dimethyl-Binol are used.[16]

These promising results led us to prepare a second smaller library of ligands focusing on the hits of the first one—16 ligands derived from 3,3′-dimethyl-Binol (Figure 3). In addition to the hits from the first screening, *i*-PrNH_2 and *t*-BuNH_2 (**B1** and **A1**, respectively) 12 other aliphatic amines were included, 6 of them with an α-alkyl substitution. Since monodentate phosphites are relatively similar to monodentate phosphoramidites, particularly the phosphoramidites based on primary amines, and since Reetz and Mehler have demonstrated that monodentate Binol-based phosphites are also excellent ligands in Rh-catalyzed hydrogenations,[17] two α-branched aliphatic alcohols (*i*-PrOH at **C2**, and *t*-BuOH at **G2**) were included in this second focused library.[18] The ligands obtained from this secondary library were tested under the same conditions as before, and the results are presented in Figure 3. As can be

(16) We already demonstrated that phosphoramidites based on 3,3′-disubstituted biphenol or binaphthol could exhibit quite different behavior than their corresponding unsubstituted analogues. Giacomina, F.; Meetsma, A.; Panella, L.; Lefort, L.; de Vries, A. H. M.; de Vries, J. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 1497–1500.

(17) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889–3890.

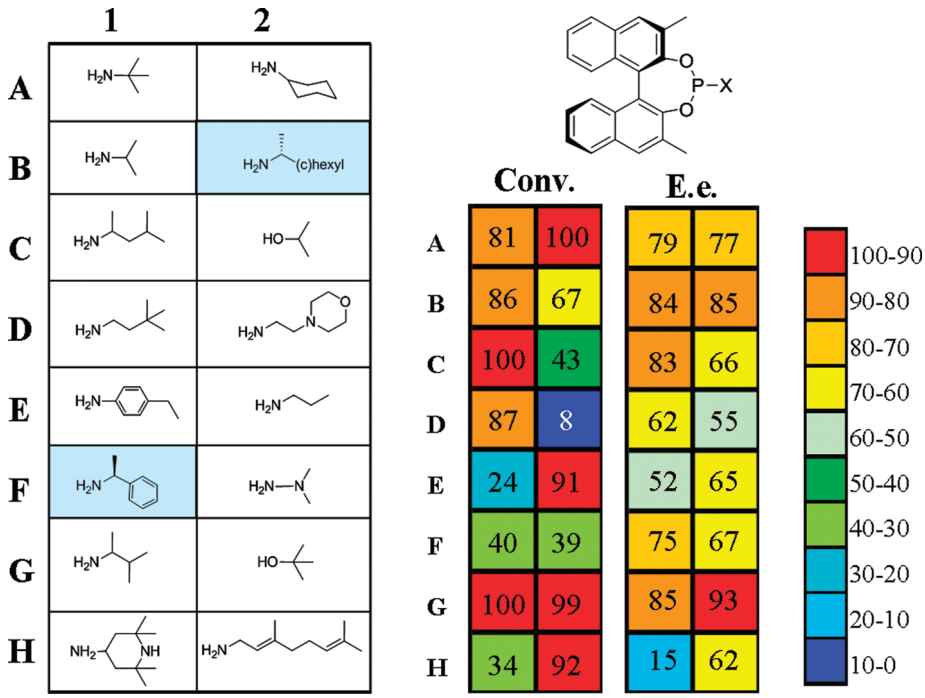


Figure 3. **Set of amines (blue = enantiomerically pure) and alcohols used to prepare the focused library and results of the screening of this library of the 16 ligands. (Reaction conditions: Rh(COD)L_2BF_4, 25 °C, 25 bar H_2, [3] = 0.073 M in dry EtOH, 3/Rh = 50 mol/mol, reaction time = 3 h).**

seen from the predominance of red- and orange-coloured cells, the ligands in this second library performed much better than the ones in the first screening. The good result obtained with *i*-PrNH_2-based ligand was confirmed (**B1**, 86% conv., 84% ee), but gratifyingly, better results were also obtained. Several phosphoramidite ligands (**C1**, **A2**, and **G2**) led to full conversion and induced enantioselectivities of ~85%, whilst the phosphite ligand based on *t*-BuOH gave the best performance (**G2**, 99% conv., 93% ee). Having a closer look at these results, it is apparent how sensitive the outcome of the hydrogenation is to small variations in the structure of the ligand. For example, the phosphite based on *i*-PrOH (**C2**) led to only 43% conv. and 85% ee. Overall, the use of aliphatic amines lacking α-substitution (**D1**, **D2**, and **E3**) never resulted in ee's above 65%, whereas those with an α-alkyl group always led to an ee in excess of 75% with the exception of **H1** which is rather peculiar due its additional N group.

Scale-Up of the Hits (G1 and G2). Both ligands were prepared on a larger scale following a procedure similar to the one used for the library, i.e. without complete purification/isolation but a simple filtration to remove the insoluble $Et_3N{\cdot}HCl$ generated during the condensation reaction. These ligands (**G1**, **G2**) were tested in an Endeavor experiment along with the pure 3,3′-dimethyl-Binol monophos (Figure 4, **L1**).

As can be seen in Figure 4, the results obtained in the library were confirmed by an Endeavor experiment in terms of enantioselectivity. Since the reaction was run for a shorter time, we were able to observe a difference of activity between the phosphoramidite **G1** and the phosphite **G2**, the latter appearing much more active. Interestingly, the catalyst based on **L1,** a

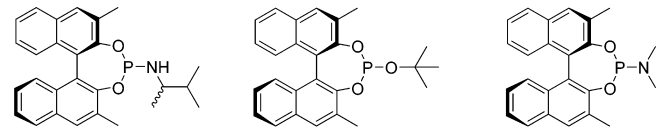


Figure 4. **Ligands used and results obtained in the Endeavor reactor. Conditions: 25 °C, 25 bar H_2, [3] = 0.091 M in dry EtOH, Rh$(COD)_2BF_4$, ligand/Rh = 2 mol/mol, 3/Rh = 50 mol/mol, reaction time = 2 h.**

highly successful ligand in other applications,[14] did not convert enamide **3**, confirming again the need to always tune the ligand to the substrate. Due to its higher activity and enantioselectivity, the phosphite **G2** was chosen as sole candidate to go further along the validation process.

Gram-scale amounts of **G2** were easily prepared using the so-called reverse synthesis where PCl_3 is first reacted with one equivalent of *t*-BuOH, followed by the reaction with (*R*)-3,3′-dimethyl-Binol. This methodology developed by van Leeuwen and co-workers was shown to be more efficient for the coupling of bulky partners (i.e., bulky Binol with bulky amines or alcohols) to the phosphorus.[19] The catalyst Rh$(COD)(\mathbf{G2})_2BF_4$ was also prepared on gram scale in a straightforward manner by simply mixing the ligand and the Rh precursor in DCM. Precipitation of the catalyst was achieved by addition of heptanes. The freshly preformed catalyst was tested in the Endeavor reactor under a number of different reaction conditions (Table 1).

A slightly better ee was obtained with the isolated catalyst (Table 1, entry 1) compared to the previous results. *i*-PrOH and

(18) When this work was done, DSM had a non-exclusive license from the Max Planck Institute in Mülheim an den Ruhr, Germany, for the use of monodentate phosphites in asymmetric hydrogenation processes.

(19) van Rooy, A.; Burgers, D.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 492–498.

Table 1. **Hydrogenation conditions and conversion/enantioselectivity[a]**

entry	solvent	*P* (bar)	*T* (°C)	conv. %	ee %
1	EtOH	25	25	100	97
2	*i*-PrOH	25	25	100	97
3	EtOAc	25	25	100	99
4	EtOH	5	25	100	98
5	EtOH	5	40	100	97
6	EtOH	5	60	100	95

[a] Conditions: [**3**] = 0.091, Rh(COD)(**G2**)$_2$BF$_4$, **3**/Rh = 50 mol/mol, reaction time = 2 h, 5 mL of solvent.

EtOAc are equally suitable solvents (entries 2 and 3) although the enantiomeric excess is a little bit higher in EtOAc. The reaction proceeds also well under 5 bar of hydrogen (entry 4). Increasing the temperature does not lead to a significant drop in the enantioselectivity and consequently high turnover frequencies should be attainable even at a pressure of 5 bar. Prior to the kilogram production in the pilot plant, a 50-mL autoclave experiment was performed with a higher S/C ratio to have an indication of the TOF. The conditions were as follows: Rh(COD)(**G2**)$_2$BF$_4$, [**3**] = 6.9 wt %, **3**/Rh = 521 mol/mol, 50 mL EtOAc as solvent, 5 bar H_2, 50 °C, 700 rpm. After 1.5 h, the conversion was 82% (97.5% ee) corresponding to an average TOF around 250 h^{-1}. A second analysis performed after 17 h showed full conversion and an ee of 97.1%. At this stage, we considered the catalyst to be validated, and the technology was transferred to the pilot plant for kilogram-scale production.

Preparation of the Prochiral Substrate 3 and Large-Scale Hydrogenation. Substrate **3** used for the catalyst screening was provided by Merck. Whilst looking for a suitable catalyst for the hydrogenation of **3**, we also investigated the scalability of the route towards **3** for production at kilogram scale. Aryl enamide **3** can be prepared in two steps starting from a CBZ-dihydropyridine chlorobenzonitrile **5** (Scheme 3).[7b] The synthesis involves the hydrogenation of the dihydropyridine substituent with the Wilkinson catalyst, exchange of the *N*-protecting group, and a direct preparation of the enamide by reaction with MeLi and acetic anhydride. Development work allowed us to improve the process and make it fit for our 25-L reactor. Notably, the amount of expensive Wilkinson catalyst was lowered by a factor of 2.5. Ultimately, starting from 2.2 kg of **5**, we were able to obtain around 1.1 kg of enamide **3**. This material was isolated from the reaction mixture as a solid by crystallization from EtOH/H_2O.

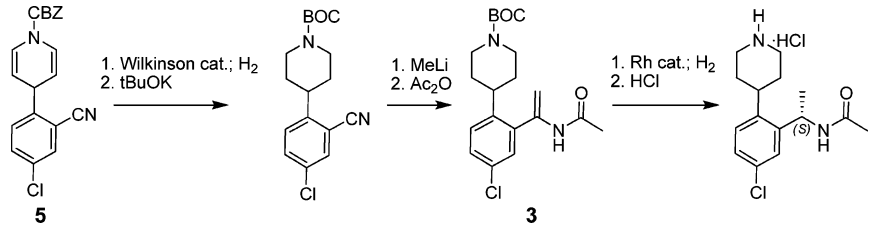
Since the initial lab tests of the obtained material were not satisfying[20] and analysis showed traces of Rh due to the Wilkinson hydrogenation (measured to be as high as 1160 ppm), a recrystallization was carried out by dissolving the crude substrate in hot ethanol, treating with activated carbon, and adding H_2O to precipitate the solid (recovery yield of 93%).

The substrate was divided in two batches and hydrogenated in a 16 L autoclave using the following conditions: 0.35 mol % catalyst, 9 wt% substrate, 7.5 L *i*-PrOH, 6 bar H_2, 32 °C. Both hydrogenations proceeded well, leading to complete conversion after 20 h. The enantiomeric excess was lower than the one obtained on lab scale: 89% ee, possibly still due to remaining Rh or other impurities.[21] The two batches were combined for removal of the N-Boc protecting group and crystallization as follows: After the hydrogenation, the reaction mixture was treated with activated carbon, followed by 5 N HCl in IPA at 50 °C. Upon cooling down, the final product, i.e. the HCl salt (Scheme 3), was isolated as an off-white solid (yield: 84%, purity: 96 wt %). The enantiomeric excess increased to 98.9%, but the amount of residual Rh (83 ppm) made a rework necessary. After a second treatment with activated carbon, the solid was crystallized from EtOH/CH_3CN leading to a final product meeting the specifications in terms of purity (99.6 area %), enantioselectivity (99.9% ee) and Rh content (3 ppm). Crystallization without charcoal treatment only lowered the Rh content to 33 ppm.

Conclusion

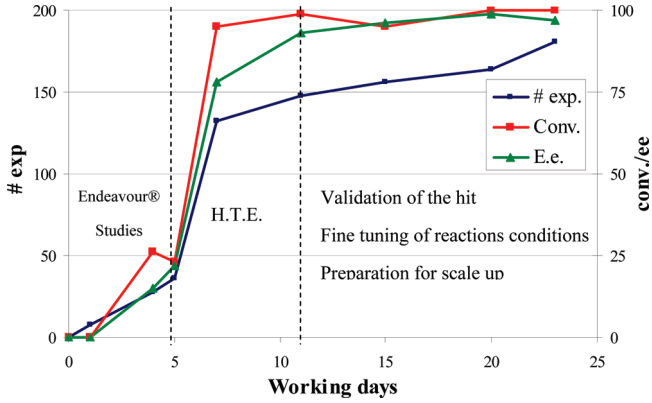
High throughput experimentation (HTE) associated with our automated ligand synthesis of chiral monodentate phosphoramidites/phosphites were key success factors for the discovery of an efficient catalyst within the short time frame available for this project. Scheme 4 represents the progress of the project versus the time. Both the cumulated number of experiments and the conversion/enantioselectivity of the best catalytic system at the moment are plotted on this graph. The project started with a few experiments to gain an impression of the hydrogenation behavior of the new substrate. A major improvement was achieved in slightly more than a week thanks to the use of the high throughput protocol. The last two weeks of the project were dedicated to preparing the ligand and catalyst at gram quantities, optimizing its performance, and determining the activity and enantioselectivity at 50 mL scale. Not surprisingly, the improvement of the catalytic system was related to the number of experiments, and it can be concluded that the project would not have been successful in such a short time span without the use of HTE. Due to its ease of synthesis, the ligand was easily produced on gram scale. Although the performance of the catalyst was not as good on pilot-plant scale as in the lab, it allowed the synthesis of the desired chiral amide on kilogram scale.

Scheme 3. **Synthetic route towards prochiral enamide 3**



5 **3**

Scheme 4. **Progress of the project (activity and ee of the best catalytic system at the time; cumulated number of experiments performed) versus time (days)**



Experimental Section

General. All laboratory-scale reactions were performed in a dry nitrogen atmosphere using standard Schlenk techniques or in the glovebox. Anhydrous solvents over molecular sieve purchased from Fluka were systematically used. Amines (generally >99%) were used as provided by Aldrich, Fluka, Acros. Binol, octahydro-Binol and 3,3′-dimethyl-Binol based phosphorus chloride were prepared according to a published procedure.[22] $Rh(COD)_2BF_4$ was provided by Umicore and Heraeus.

Synthesis of G2, (*R*)-3,3′-Dimethylbinapthyl-*tert*-butoxy-phosphite. Stock solutions of the different reagents are prepared as follow: 1.577 g of PCl_3 (11.5 mmol) is dissolved in 10 mL of dry toluene. 0.847 g of *tert*-butanol (11.5 mmol) is dissolved in 10 mL of dry toluene. 1.23 g of Et_3N (12.2 mmol) is dissolved in 10 mL of dry toluene. The stock solutions are brought in the glovebox. The solutions of *tert*-butanol and Et_3N are mixed together and added slowly to the solution of PCl_3. The reaction mixture is left to stir for 1 h. 3.614 g of (*R*)-3,3′-dimethyl-Binol (11.5 mmol) is dissolved in 5 mL of dry toluene, together with 2.308 g of Et_3N (22.85 mmol). The Binol solution is slowly added to the reaction mixture and left to stir for 45 min. The reaction mixture is then filtered on a glass frit (P4), the left-over solid are washed with 2 × 15 mL dry toluene. The filtrates are split in two batches. One batch is kept in the glovebox. The other is taken out of the glovebox to the vacuum line where the solvent is evaporated under vacuum from around 50 mL to about 5 mL. 20 mL of pentane is added to the solution, yielding a small amount of precipitate, which is filtered off. The filtrate is collected and the solvent is evaporated under vacuum, yielding a white sticky solid. ^{1}H NMR (toluene-d_8) δ: 7.88−7.11 (m, 10H), 2.85 (s, 3H), 2.77 (s, 3H), 1.54 (s, 9H); ^{31}P NMR δ: 155.5.

Synthesis of (COD)Rh(G2)$_2$BF$_4$. In the glovebox, $Rh(COD)_2BF_4$ (2.69 g, 6.62 mmol) is dissolved into 25 mL of dry DCM. The phosphite **G2** (6.04 g, 14.5 mmol, 2.2 equiv/Rh) dissolved in 25 mL of dry DCM is added dropwise to the Rh solution over a period of 30 min. The dark-red solution turns bright orange after addition of all the ligand. The mixture is stirred for 2 h extra, and heptane is added, leading to the precipitation of an orange solid (5.99 g, yield = 80%).

Hydrogenation of Enamide 3 in a 150-mL Autoclave. $Rh(COD)(\mathbf{G2})_2BF_4$ (23 mg, 0.02 mmol) is placed in a Schlenk tube under N_2 and dissolved in 4 mL of dry degassed DCM. A 150-mL Parr autoclave is loaded with 3.98 g of enamide **3** (10.5 mmol). The autoclave is closed and purged with N_2. Dry, degassed EtOAc (50 mL) is added. The mixture is stirred for a few minute prior to the addition of Rh catalyst solution (S/C = 530). The autoclave is purged with N_2 and H_2 filling/emptying cycles. The reactor is pressurized with 5 bar of H_2 and heated to 50 °C. Once this temperature is reached, the reaction is stirred at 700 rpm The hydrogenation is stopped after 17 h, and analysis is performed using chiral HPLC. Conversion = 100%, 97.1% ee.

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Supporting Information Available

Experimental procedure for the preparation and testing of the libraries of ligands and for the large-scale hydrogenation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Purity of the substrate is crucial to have a smooth asymmetric hydrogenation, as also described by Merck for this substrate, see ref 9. Note that at the time of this investigation the purification work of enamide **3** was not yet published, nor known to us.

(21) The lower ee value obtained here is caused by a suboptimal purification of the substrate due to tight deadlines for the delivery of the final product. However, these results made us feel confident that our process was fitted for large-scale production since improvements both in terms of substrate-to-catalyst ratio and enantiomeric excess are common in successive production campaigns.

(22) de Vries, A. H. M.; Pineschi, M.; Arnold, L. A.; Imbos, R.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620.