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A Mixed-Ligand Approach Enables the Asymmetric Hydrogenation of an α-Isopropylcinnamic Acid en Route to the Renin Inhibitor Aliskiren

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Abstract:

An asymmetric hydrogenation process for the α-isopropyl dihydrocinnamic acid derivative 2, an intermediate for the renin inhibitor aliskiren (4), has been developed using a rhodium catalyst ligated with a chiral monodentate phosphoramidite and a nonchiral phosphine. Whereas catalysts based on two equivalents of monodentate phosphoramidites gave promising results, the rate of hydrogenation and ee of the product could be improved spectacularly by the addition of monodentate nonchiral triarylphosphines to these catalysts. This remarkable mixed-ligand catalyst has been identified using high-throughput experimentation. With the best catalysts turnover numbers >5000 mol mol^{-1}, turnover frequencies >1000 mol mol^{-1} h^{-1}, and ee's up to 95% have been achieved.

Introduction

Asymmetric hydrogenation is one of the early success stories of the application of homogeneous catalysis in fine chemicals production.[1] The L-DOPA process that earned Knowles his Nobel Prize was developed in the early 1970s.[2] Yet, in the years after, not many other asymmetric hydrogenation processes were implemented.[3] We and others have analysed the obstacles that stood between this wonderful technology and its use in production.[3,4] There are several critical issues involved with asymmetric hydrogenation of which (i) the overall costs for the catalytic transformation—mainly the metal and the ligand but also the substrate which may need to be highly pure—and (ii) the time-to-market pressure in the development of processes for new pharmaceutical entities are the most important ones. In the mean time, we have come a long way towards solving these two major hurdles by the development of cost-effective and modular synthesized monodentate ligands (MonoPhos)—in collaboration with the group of Feringa and Minnaard[5]—and implementation of high-throughput experimentation (HTE) techniques,[4,6] including the development of methodology for automated parallel synthesis of these ligands.[6,7] This parallel protocol, in which 96 new ligands are synthesized and tested within 2 days, is now routinely used by DSM Pharmaceutical Products for the screening of customer requests.

During the development of this automated protocol we were faced with the challenge to find a more cost-effective catalyst for the asymmetric hydrogenation of the α-isopropylcinnamic acid derivative (**1**), which is an intermediate in Novartis' new blood pressure-lowering agent aliskiren (**4**), the first oral renin inhibitor (Scheme 1).[8,9] This route to synthon A (**3**) with the key asymmetric hydrogenation step has been developed recently.[10] The catalyst is based on a ferrocene-based bisphosphine ligand called Walphos,[11] which is prepared in five steps from the Ugi amine.[10a] Although

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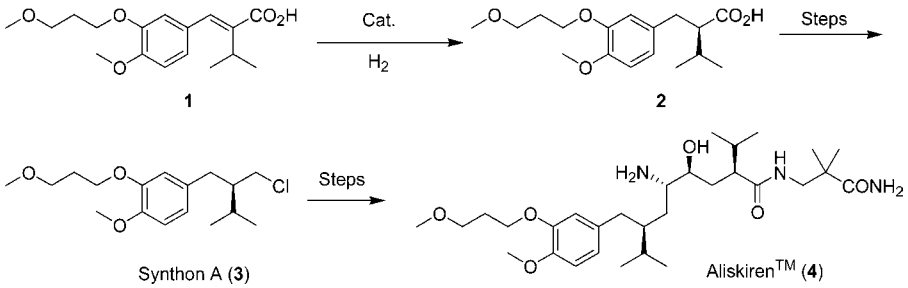
Scheme 1. **Asymmetric hydrogenation in the synthesis of aliskiren**



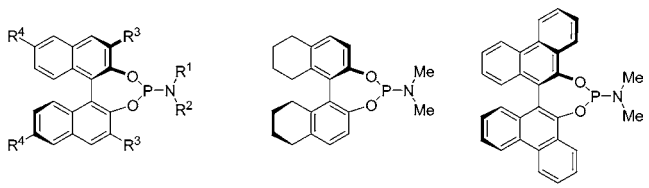
the reaction effectively produces the product with 95% ee at a substrate/catalyst ratio (S/C) of 5000, we felt that the use of a monodentate phosphoramidite ligand could lead to substantial cost savings.

Part of the work described in this paper has been communicated earlier as part of a concept article.[6a]

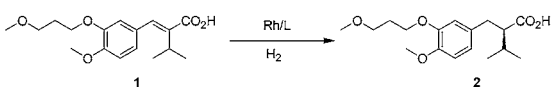
High-Throughput Screening Approach. Since most successful asymmetric hydrogenations of α,β-unsaturated carboxylic acids are described with catalysts derived from ruthenium[12] and in view of the above results,[11] we started our screenings with both $[Ru(cymene)Cl_2]_2$ and $RuCl_3$ and $[Rh(COD)_2]BF_4$ as catalyst precursors using the parent MonoPhos and eight other phosphoramidites as ligands (Figure 1, **5a**−**g**, **6**, and **7**). The best results from this preliminary screening were obtained with rhodium catalysts, at 20 bar hydrogen pressure in isopropanol at 85 °C (Figure 2).

Although the enantioselectivities obtained in these experiments were not as good as the published results, we were confident, on the basis of past experience, that further optimisation using the "instant ligand library" protocol would allow us to find a ligand that induces sufficiently high enantioselectivity. What worried us more was the rate of the reaction, which needed to be improved rather drastically to achieve a cost-effective process.

Upon looking for trends in Figure 2 we found that the positive effect of the 3,3′-disubstitution pattern (ligands **5e** and **5f**) on the rate is clearly discernible. Whereas the rhodium catalyst based on ligand **5e** was relatively slow for the hydrogenation of methyl 2-acetamidocinnamate as compared to the MonoPhos-based catalyst,[5b] here we see just



5a $R^1 = R^2 = Me$, $R^3 = R^4 = H$ (MonoPhos) **6** **7**
b $R^1 = R^2 = CH_2Ph$, $R^3 = R^4 = H$
c $R^1 = Me$, $R^2 = CH_2Ph$, $R^3 = R^4 = H$
d $R^1 = H$, $R^2 = (R)$-$CH(CH_3)Ph$, $R^3 = R^4 = H$
e $R^1 = R^2 = Me$, $R^3 = Me$, $R^4 = H$
f $R^1 = R^2 = Me$, $R^3 = Ph$, $R^4 = H$
g $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Br$
h $R^1 = R^2 = -(CH_2)_5-$, $R^3 = R^4 = H$ (PipPhos)
i $R^1 = R^2 = -(CH_2)_5-$, $R^3 = Me$, $R^4 = H$



1 2

Figure 1. **MonoPhos ligands.**

the reverse. Fortunately, ligand **5e** also induces the highest enantioselectivity.

The relatively low rate of the reaction is related to the fact that phosphoramidite ligands, although good π-acceptors, are poor σ-donors. Since oxidative addition of hydrogen is the putative rate-determining step, ligands that donate charge will accelerate the transition of Rh(I) to Rh(III). Fortunately, the use of monodentate ligands creates the opportunity to screen for additives or ligands, which could conceivably donate more electrons to the Rh−phosphoramidite complex, and hence make it more active. In Figure 3 the results are shown of a rather random screening of phosphines, bisphosphines, and several types of nitrogen-containing ligands that were added to the rhodium/MonoPhos precursor. This screening was carried out using a liquid dispensing robot in the glovebox to prepare the solutions containing catalysts, additives, and substrates. The actual hydrogenation was carried out in the Premex 96, an autoclave capable of handling 96 vials at the same time.

These results immediately confirm the power of the high-throughput experimentation approach: only a few of these experiments gave interesting results, which would not have been found easily in a one-experiment-at-a-time approach. Addition of triphenylphosphine, tri-*p*-tolylphosphine or tri-*p*-anisylphosphine (all relatively electron rich) led to a remarkable acceleration (full conversion) and ee's of a promising level,[13] whereas addition of triarylphosphines substituted with halogens are less accelerating and moreover give rise to racemic product. Most of the tested bisphosphines also accelerate, but here the low ee's suggest that maybe the monodentate phosphoramidites have been replaced by the nonchiral or racemic bisphosphines. Nitrogen-based additives were uniformly ineffective.

Since these results were obtained with the parent MonoPhos ligand, we decided to test the effect of the added phosphine for other Rh catalysts based on other phosphoramidite ligands, in particular the 3,3′-disubstituted ones.

The results of this run depicted in Figure 4 confirm that the positive effect of added triphenylphosphine on the rate and enantioselectivity is universal for the tested phosphoramidites. Again, the 3,3′-disubstituted ligands gave the most

(12) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 1, p 21.
(13) These experiments are the first instance in which we have used a mixed-ligand catalyst (July 2002). The usefulness of this approach is quite general and has also independently been shown by Reetz and coworkers: (a) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed*. **2003**, 42, 790. (b) Reetz, M. T.; Mehler, G. *Tetrahedron. Lett*. **2003**, *44*, 4593. (c) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem*. **2003**, *1*, 1087.

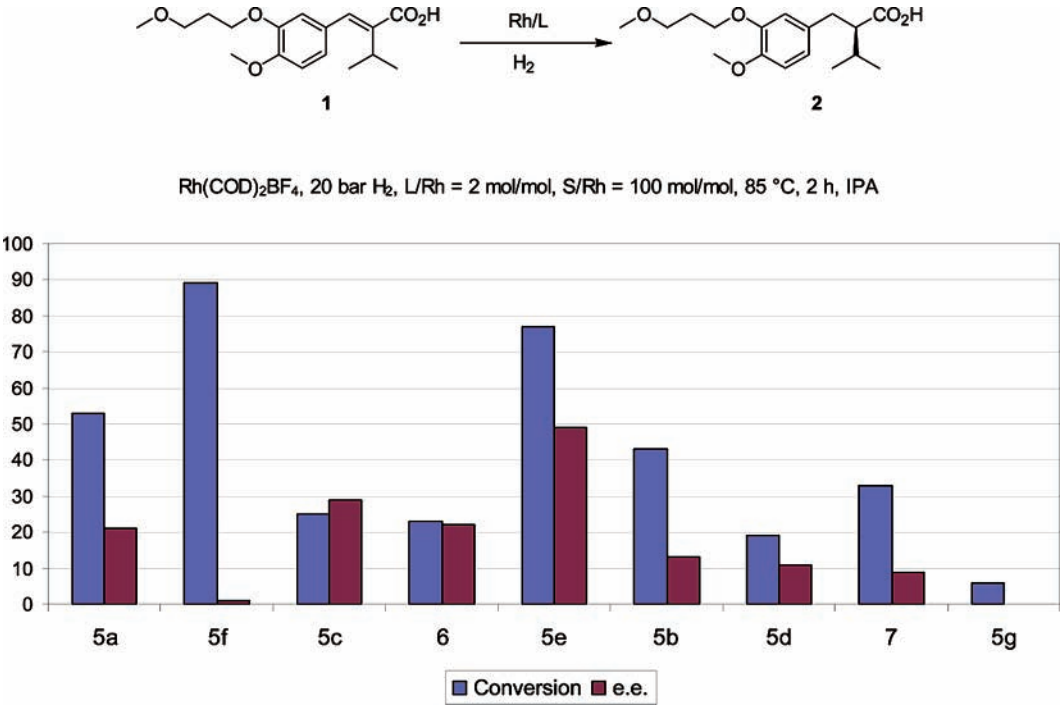


Figure 2. **Initial screening of phosphoramidite ligands in the Rh-catalysed hydrogenation of 1.**

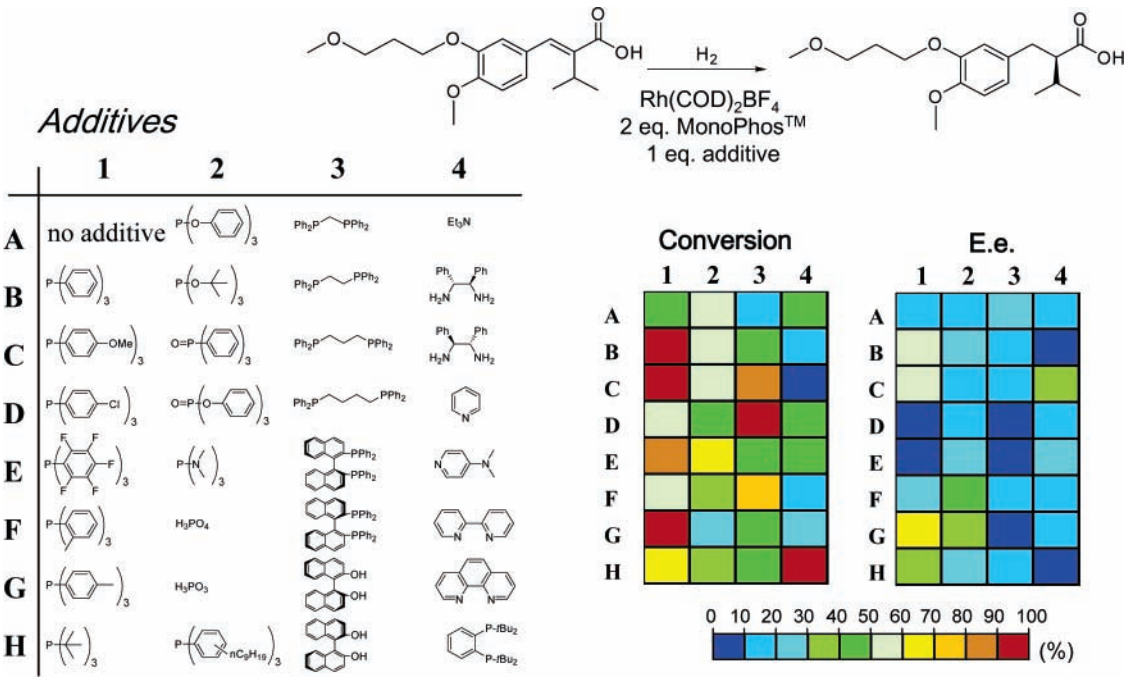


Figure 3. **Screening of 31 additives in the Rh/MonoPhos-catalysed hydrogenation of 1.**

interesting results: 75% ee for the 3,3′-diphenyl-substituted ligand mixed with PPh_3 (racemic without PPh_3!) and 80% ee for ligand **5e** (3,3′-dimethyl ligand). The scope of the mixed-ligand hydrogenation of α-alkylated cinnamates and acrylates has been further explored in collaboration with Feringa/Minnaard.[14]

The triphenylphosphine effect can be explained by assuming the phosphine is bound to the metal complex. This in turn evokes the question of the stoichiometry. If we assume that only two ligands can be bound to rhodium in its active state, the following complexes may be formed (PA = phosphoramidite; TPP = triphenylphosphine):

$$[Rh(PA)_2]^+ \rightleftharpoons [Rh(PA)TPP]^+ \rightleftharpoons [Rh(TPP)_2]^+$$

The increased rate *and* enantioselectivity can only result from the formation of the mixed complex. Thus, formation of this complex needs to be optimised. In the next experiments we have systematically varied the Rh/PA/TPP ratio. Results are depicted in Table 1.

(14) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4209.

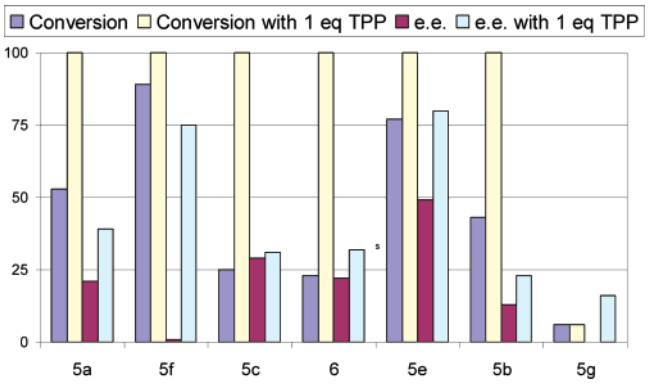


Figure 4. **Asymmetric hydrogenation of 1 with $[Rh(COD)_2]BF_4$/2L/1PPh_3.**

Table 1. **Effect of phosphoramidite/triphenylphosphine ratio**

entry	PA/Rh	TPP/Rh	conv. (%)	ee (%)
1	3.6	1	63	76
2	2	1	100	80
3	2	2	100	78
4	2	3	100	76
5	2	5	100	75
6	1	3	100[b]	59
7	1	2	100[b]	66
8	1	1	100[b]	76
9	2	0.4	100[b]	80

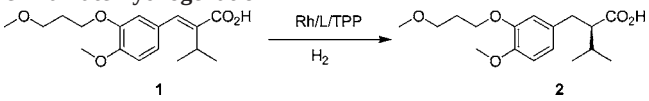
[a] Conditions: substrate/rhodium ratio of 100, solvent is *i*-PrOH, 20 bar of hydrogen, 2 h reaction time at 85 °C unless stated otherwise. [b] Only measured after 18 h of reaction time.

As can be seen from the results, any presence of TPP in the catalyst mixture enhances the activity and enantioselectivity compared with the $Rh(PA)_2$ complex; however, the enantioselectivity is the highest if the ratio between PA and TPP is 2 or larger. With a Rh/PA/TPP ratio of 1:2:1 the formation of the non-enantioselective, but active, $Rh(TPP)_2$ complex is prevented.[15]

At this stage we were all excited about the positive nonchiral phosphine effect, but the enantioselectivity was still not high enough for application. Fortunately, a second important breakthrough was found when the reaction conditions, solvent and temperature, were optimised using the mixed-ligand system. As in the initial screening the results obtained with non-protic solvents, e.g., dichloromethane, were disappointing; however, adding water to isopropanol (20−60 v/v%) enhanced the enantioselectivity up to a staggering 95% at 25 °C (Table 2). The ee is nearly independent of the water concentration, in contrast to the activity. It decreases drastically at water concentrations above 40 v/v%, due to solubility problems of the substrate. The exact role of water is not clear at this stage, but we assume it may have a positive effect in association and dissociation of the substrate and product, respectively.

(15) Confirmed by ^{31}P NMR, see: (a) Hoen, R. *New Approaches in Asymmetric Rhodium-Catalyzed Hydrogenations with Monodentate Phosphoramidites.* Ph.D. thesis, University of Groningen, 2006. The optimal ratio in this mixed-ligand approach needs to be determined for every new substrate and every new ligand. For a discussion and a mathematical model see: (b) Gennari, C.; Monti, C.; Piarulli, U.; de Vries, J. G.; de Vries, A. H. M.; Lefort, L. *Chem. Eur. J.* **2005**, *11*, 6701.

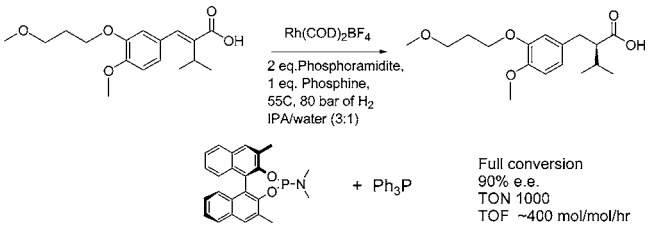
Table 2. **Effect of water/*i*-PrOH on the Rh-catalysed cinnamate hydrogenation[a]**



entry	vol % water in *i*-PrOH	conv. (%)	ee (%)
1	0	86[b]	85
2	20	62	93
3	30	67	94
4	40	67	94
5	50	100[b]	92
6	50	55	95

[a] Conditions: substrate/rhodium ratio of 100, 3,3′-dimethyl-MonoPhos/rhodium ratio of 2, TPP/rhodium ratio of 1, 20 bar of hydrogen, 4 h reaction time at 25 °C unless stated otherwise. [b] Only measured after 18 h of reaction time.

Scheme 2. **Validation of screenings results in 150-mL autoclave**



Validation and Pilot-Plant Run. After this screening exercise and the identification of a highly promising catalyst, we wanted to validate these results at a larger scale (autoclaves between 150 and 450 mL) using scaleable conditions. The most important parameters for large-scale application are the concentration, turnover number (TON), and activity (TOF), all related with the cost-determining "space-time-yield" factor. Since higher hydrogen pressure and higher temperature are advantageous for the activity, but disadvantageous for the enantioselectivity, we decided to use

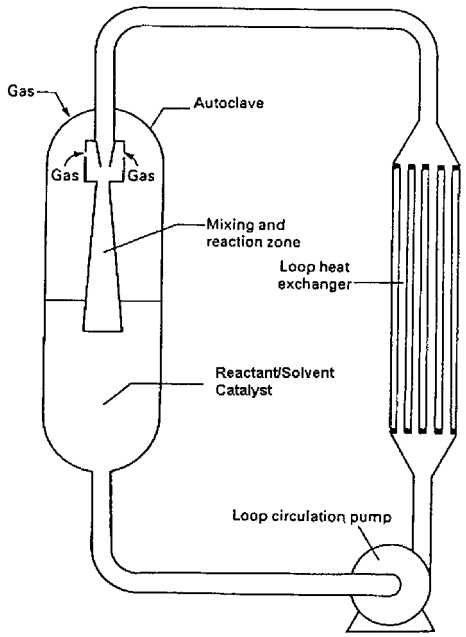


Figure 5. **Schematic drawing of a Venturi loop reactor.**

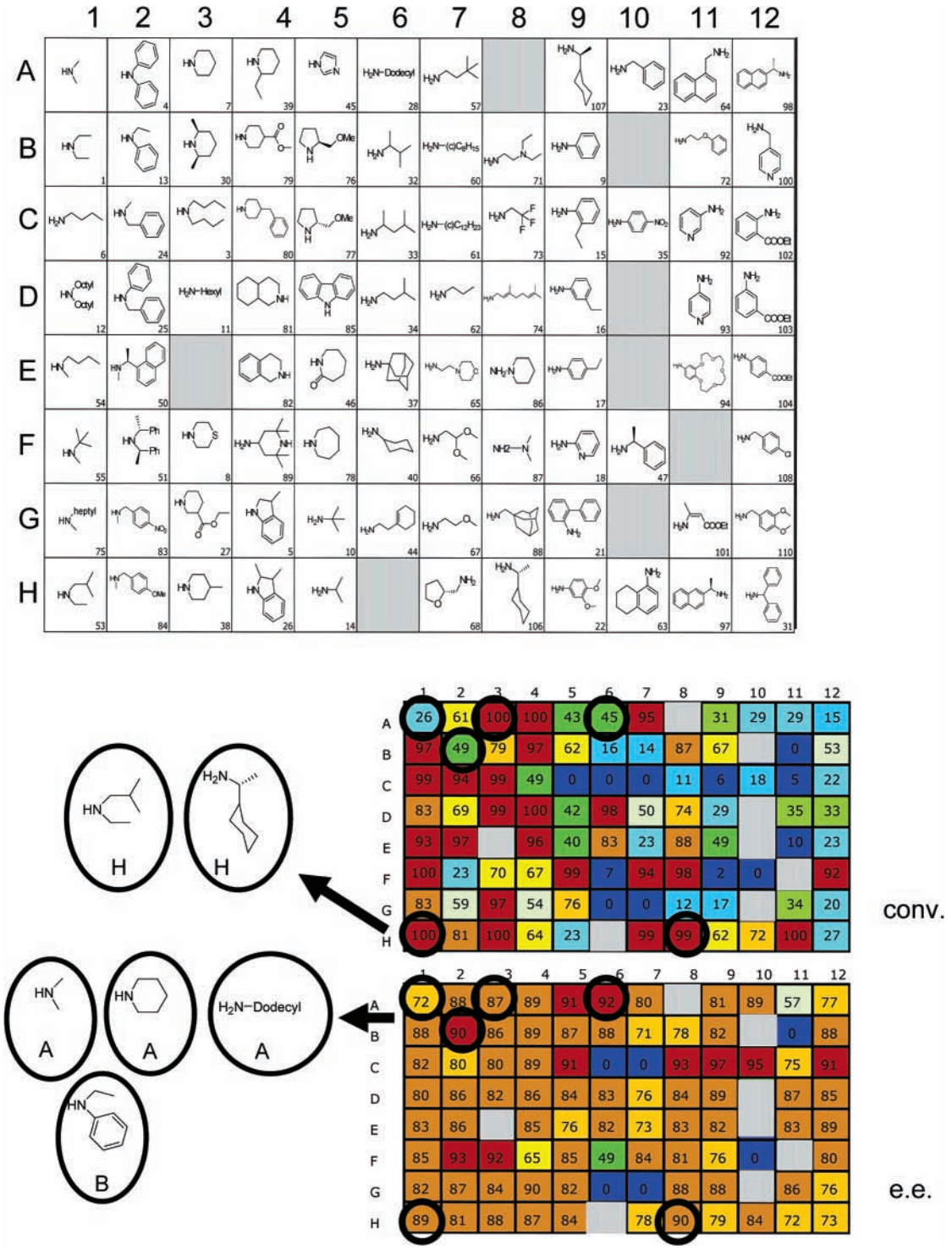


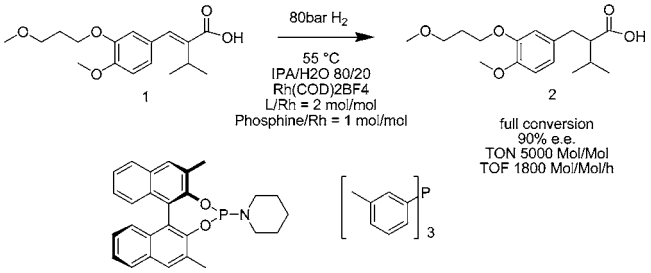
Figure 6. **Screening of monodentate phosphoramidite ligands based on 3,3′-BINOL in the Rh-catalysed hydrogenation of 1 with TPP as additive. (Conditions: 55 °C, 25 bar H_2, in *i*-PrOH, $[Rh(COD)_2]BF_4$, 1/Rh = 100, ligand/Rh = 2, TPP/Rh = 1.)**

the compromise conditions depicted in Scheme 2, furnishing the product with 90% ee (at 55 °C and 80 bar of hydrogen).

The next items to be developed were the scale-up of the chiral ligand synthesis, and the optimisation of the catalyst formulation and addition. Whereas the first item was tackled quite straightforwardly, some special requirements were needed for the catalyst formulation and addition. Unfortunately, these cannot be disclosed at this stage of the project.[16] Interestingly, by using this chiral ligand derived from 3,3′dimethyl-BINOL an impurity in the product was observed by using HPLC in, at first sight, alarming high amounts (based on area %). After a moment of disappointment, the source of the problem was rapidly identified as being caused by the enormous high response factor of the BINOL fragment, formed in tiny amounts by hydrolysis of the chiral ligand.

(16) Due to confidentiality reasons full data on the scaled-up process could not be presented.

Scheme 3. **Catalyst system for the asymmetric hydrogenation of 1**



The actual pilot-plant run was performed in a loop reactor and proceeded satisfactorily, furnishing the product within specs. A loop reactor is different from a stirred tank reactor (CSTR) in that part of the liquid is pumped up continuously and sprayed though a nozzle (Venturi loop) together with the hydrogen gas, ensuring optimal mass transfer from the gas to the liquid phase. For a schematic picture, see Figure 5. However, the observed activity (full conversion after ca. 18 h at S/C ratio of 3000) should be better in order to reach an overall improved throughput ("space-time-yield"). Therefore, a second screening, now with the automated ligand synthesis protocol, was initiated.

"Instant Ligand Library" Screening. Since the 3,3′-dimethyl-BINOL moiety of the chiral ligand was crucial for high ee and activity, we decided to screen a library of 96 different phosphoramidite ligands all based on this diol. The conditions used for this screening (see Figure 6) were slightly different from the optimal ones used above since water was, at that time, not tolerated in our automated ligand library setup.

As can be seen, a wide variety of primary and secondary amine-derived ligands were tested, giving a wealth of information. A few conclusions can be drawn:

(a) 10−15% of the ligands are not formed, due to steric hindrance and/or impurities (confirmed by ^{31}P NMR).

(b) In general the ligands derived from secondary amines (columns 1−5) lead to higher yields in this specific hydrogenation than the ones derived from primary amines (columns 6−12).

(c) Almost all ligands induced a medium-to-high ee, indicating that the 3,3′-dimethyl-BINOL part is the determining moiety for enantioselectivity.

(d) Most ligands prepared in this screen led to better results as obtained with the ligand used above (A1, not in situ prepared but added as such). Note that these results were obtained without addition of water.

The five best ligands in terms of enantioselectivity and activity (encircled in Figure 6), (together with the ligand used earlier) were tested with 16 triarylphosphines (experiments and results are not shown). Although the highest ee's were found with tri-*o*-anisylphosphine combined with several of the phosphoramidites derived from secondary amines, the best performance (combination of activity and enantioselectivity) was found for the 3,3′-dimethyl-PipPhos ligand (**5i**) mixed with tri-*m*-tolylphosphine. This final result of this screening effort was again validated as shown in Scheme 3. Compared with that of the catalyst used in the pilot plant the activity is more than 4 times as high.

Validations. The excellent performance of the catalyst prepared from 3,3′-dimethyl-PipPhos (**5i**) and a nonchiral phosphine was also seen at larger scale. As can be seen from Figure 7,[17] the rate of asymmetric hydrogenation is first order in rhodium concentration at relative high rhodium concentrations. At lower amounts of rhodium the reaction times are longer than one would expect for a linear relation, most likely due to catalyst deactivation caused by a minor impurity in the starting material. However, even at a substrate/Rh-catalyst ratio >10,000 a full conversion has been obtained after a reasonable reaction time (Figure 8.). From these data it is also clear that in all cases the process was stable and is not suffering from substrate or product inhibition.

Conclusion

In conclusion we have developed a scaleable asymmetric hydrogenation process based on a mixed monodentate ligand approach by using a bulky phosphoramidite and triarylphos-

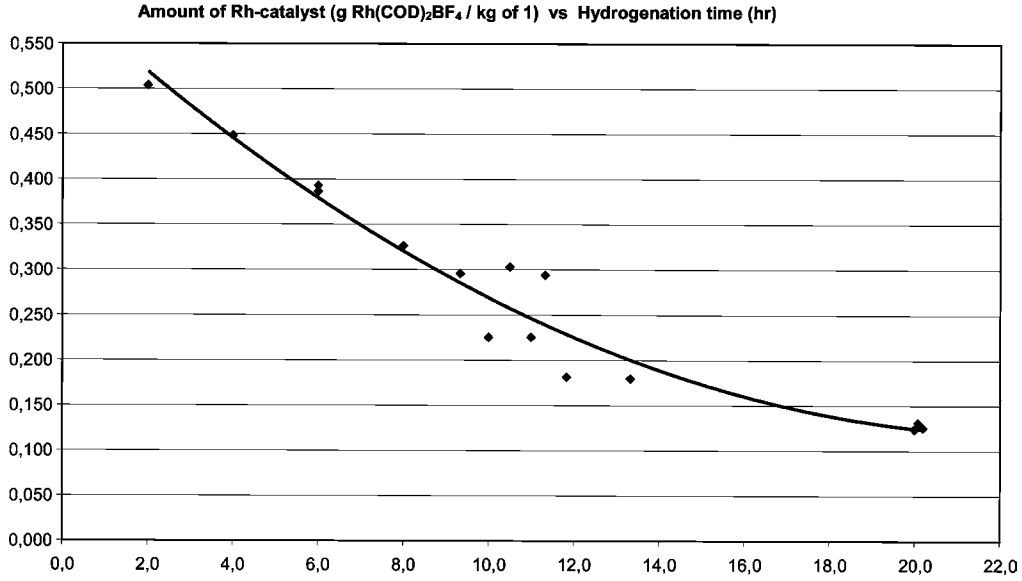


Figure 7. **Hydrogenation times required to reach full conversion at different Rh-catalyst/substrate ratios.[17]**

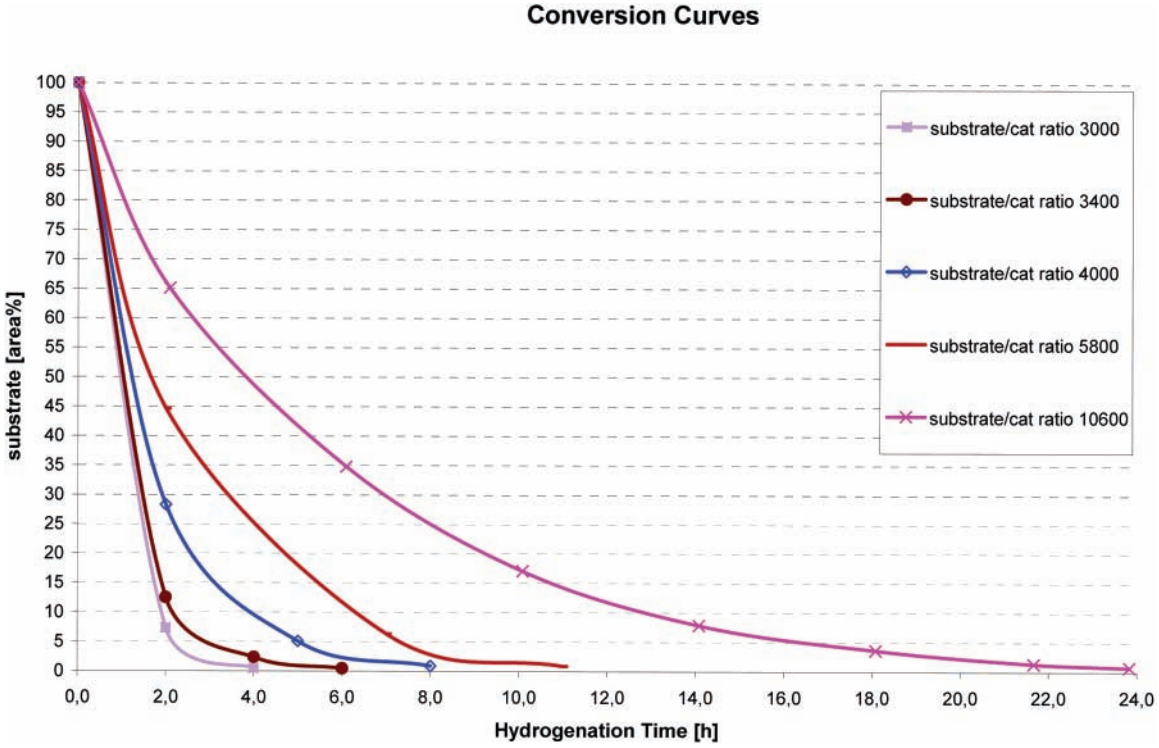


Figure 8. **Hydrogenation times required to reach full conversion at different substrate/Rh ratios.**

phine. The identification and development of this unique catalyst has been accelerated by using HTE techniques, including automated parallel ligand synthesis and parallel screening. We have proven that this approach with a virtual *unlimited* ligand library delivers scaleable asymmetric hydrogenations and are confident that we can disclose other examples in the near future.

Experimental Section

Screening experiments in the Endeavor were performed on a 5-mL scale. For this all the solid substances were weighed in the glass insert tubes in air, which were then placed in the apparatus. The apparatus was closed and flushed 10× with 3 bar N_2. Then degassed solvent (3 vacuum/N_2 cycles) was added through the injection valve. The apparatus was flushed again with 3 bar N_2 without stirring (10×), 5× with stirring, and 10× with 30 bar H_2 without stirring. Thereafter, the Endeavor was simultaneously pressurized to the desired H_2 pressure (normally 20 bar) and heated to the desired temperature under stirring at 500 rpm. The following amounts were used: 2 mM $[Rh(COD)_2]BF_4$, IPA (5 mL), ligand/Rh = 2 mol/mol, **1**/Rh = 100.

The screening procedure in the Premex96 is described in reference 7a.

(17) The spread in the middle data points is related to operator judgement of what constitutes full conversion and error due to late or early sampling as a result of shift changes.

(*R*)-3-[4-Methoxy-3-(3-methoxypropoxy)phenyl]-2-(1-methylethyl)propanoic Acid. In a 450-mL autoclave, 50 g (178.35 mmol) of *E*-3-[4-methoxy-3-(3-methoxyproxy)-phenyl]-2-(1-methylethyl)propanoic acid, 100 mg (0.234 mmol) of 3,3′-dimethyl-PipPhos, 47.6 mg (0.1172 mmol) of $[Rh(COD)_2]BF_4$ and 30.8 mg (0.117 mmol) of triphenylphosphine were suspended in 160 mL of isopropanol/H_2O (4:1). The autoclave was purged 5× with N_2 and heated to 55 °C. Next it was purged 3× with H_2 and subsequently pressurised to 80 bar with H_2 without stirring. The hydrogenation was continued at this temperature and pressure while stirring at 100 rpm. After 18 h the autoclave was allowed to come to room temperature and depressurized. The product was isolated (50 g, 97%) and the enantiomeric excess determined by HPLC; ee = 90%

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