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**PAPER**

# Asymmetric hydrogenation of C=C double bonds using Rh-complex under homogeneous, heterogeneous and continuous mode conditions†

**Szabolcs Balogh,[a] Gergely Farkas,[a] József Madarász,[a] Áron Szöllősy,[b] József Kovács,[c] Ferenc Darvas,[d] László Ürge[d] and József Bakos*[a]**

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A green process for enantioselective hydrogenation of dehydroamino acid derivatives and dimethyl itaconate with a rhodium catalyst modified by a new phosphine–phosphoramidite has been developed providing 97.7–99.8% enantioselectivity in green solvents such as ethylene carbonate and propylene carbonate. The L-DOPA precursor was obtained by simple filtration in 71% yield with 99.5% *ee*. Dimethyl itaconate was hydrogenated under solvent-free condition at 50 °C with 98.7% *ee*. The new rhodium complex was heterogenized on a mesoporous $Al_2O_3$ support using phosphotungstic acid (PTA) as an anchoring agent and tested in heterogeneous batch and flow reaction modes. The supported catalyst was reused eight times in the batch mode with over 97% *ee* and used over 12 hours in the flow reaction mode with an average of 97% *ee* in the asymmetric hydrogenation reaction of (*Z*)-α-acetamidocinnamic acid methyl ester.

## Introduction

Transition metal complexes containing chiral ligands are widely used in industrial scale for asymmetric catalytic hydrogenation. In particular, rhodium-based complexes modified with chiral phosphine ligands have been found to be excellent catalysts.[1] The discovery of novel and effective ligands is one of the key challenges for the creation of more efficient catalysts. Several hundreds of chiral ligands have been prepared and a few thousand successful examples of asymmetric hydrogenation on lab-scale have been published.[2] Traditionally, chiral bidentate phosphine ligands[2] have dominated this field until more recently Feringa *et al.*,[3] Reetz and Mehler[4] and Pringle *et al.*,[5] introduced the use of monodentate phosphites and phosphoramidites.

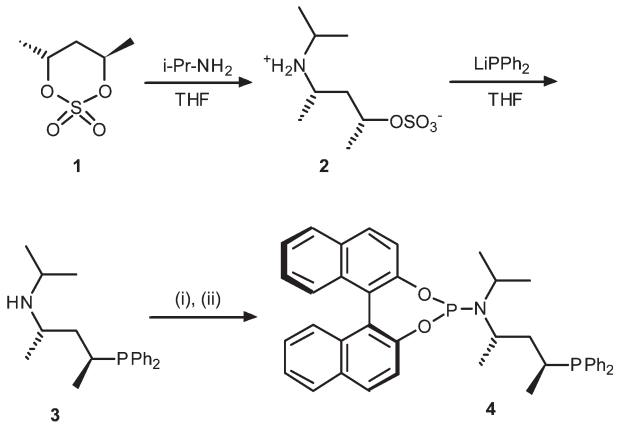
Today, the most frequently used catalysts for asymmetric hydrogenation contain phosphoramidite-type ligands. These ligands[3] are easy to prepare and they can be synthesized and applied by high throughput screening methods, however, catalysts modified with hybrid bidentate ligands provide generally better chiral induction with many of the substrates.[6] Recently, it was shown that they are applicable for a wide range of reactions, *e.g.* asymmetric hydrogenation, allylic alkylation and hydroformylation.[7] In addition to their excellent catalytic properties, these ligands were found in some cases to be air and moisture stable. However, so far only a limited number of these compounds have been developed and characterized, such as Me-AnilaPhos,[8] THNAPhos and HY-Phos,[9] ferrocenyl-containing ligands,[10] Indolphos,[11] PEAPhos[12] and QUINAPhos.[13]

Up to now organic cyclic carbonates have not played a role as solvents for asymmetric hydrogenation. The few exceptions in homogeneous catalysis include the platinum-catalyzed hydrosilylation of unsaturated fatty acids investigated by Behr *et al.*,[14] regioselective rhodium-catalyzed hydroformylation,[15] iridium- and rhodium-catalyzed asymmetric hydrogenation by Börner *et al.*,[16] palladium-catalyzed Heck reaction by Reetz and Lohmer,[17] and rhodium-catalyzed intermolecular alkyne hydroacylation.[18] In catalytic processes it would be desirable to be able to recover and to recycle the catalyst for economical and environmental viability. A promising strategy is the heterogenization of active metal complexes on an insoluble support. Many approaches have been published to "heterogenize", "immobilize" or "anchor" a homogeneous catalyst[19] by the use of polymer supported catalysts[20] and catalysts on inorganic carriers,[21] or both.[22] Covalent binding is by far the most frequently used strategy, however, a common and simple immobilization technique of catalytically active metal complexes is ionic binding, which is particularly useful for cationic rhodium[23] and palladium catalysts.[24]

Besides easy separation, immobilization opens up new opportunities such as use of continuous flow reactors[25] or further

[a]*Department of Organic Chemistry, University of Pannonia, 8200 Veszprém, Egyetem u. 10, Hungary. E-mail: bakos@almos.vein.hu*
[b]*Department of Inorganic and Analytical Chemistry, University of Technology and Economics, 1111 Budapest, Műegyetem rkp. 3-9, Hungary*
[c]*Institute of Environmental Engineering, University of Pannonia, H-8201 Veszprém, P.O. Box 158, Hungary*
[d]*ThalesNano Nanotechnology Inc., 1031 Budapest, Záhony u. 7, Graphisoft Park, Hungary*

†Electronic supplementary information (ESI) available: Supporting information for this article contains the NMR spectra of the ligand and its rhodium complex, hydrogenation experiments, preparation of [Rh(COD)(**4**)]/PTA/$Al_2O_3$, textural characterization of support, the support modified by PTA, and the immobilized complex, as well as HPLC analysis of the chiral amino acid derivatives. See DOI: 10.1039/c2gc16447g




**Scheme 1** (i) Formation of lithium amide of **2** by Li metal or BuLi. (ii) Addition of (*S*)-chlorodinaphthodioxaphosphepine to **3**.

tuning of the catalyst environment, which in some cases can lead to improved catalytic performance.[26]

In this paper, we present a detailed study demonstrating that our novel hybrid phosphine–phosphoramidite ligand provides high selectivity, even in green solvents, in the asymmetric hydrogenation reaction. The green chemistry aspects[27] of asymmetric hydrogenation are represented by switching to environmentally benign solvents and by solvent-free reactions, improved process parameters (atom economy, high chemo- and enantioselectivity, reaction efficiency, waste free workup) and continuous flow processing.

## Results and discussion

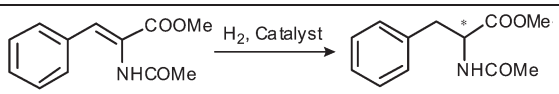
### Synthesis

The novel ligand (**4**) was synthesized in three steps (Scheme 1). At first, enantiomerically pure (4*R*,6*R*)-4,6-dimethyl-1,3,2-dioxathiane 2,2-dioxide[28] (**1**) and 2-propylamine were mixed neat or in THF leading to the amino sulfate compound (**2**).[29] The addition of (**2**) to three equivalents of $LiPPh_2$ in THF provided the aminoalkyl phosphine (**3**). Ring opening reaction of the cyclic sulfate with the amine and the second substitution reaction take place with complete inversion at the stereogenic centers providing a product with (2*S*,4*S*) configuration. Finally, lithium amide of the secondary amine was formed by addition of BuLi or Li metal.[30] The amide was then treated with (*S*)-chlorodinaphtho[2,1-*d*:1′,2′-*f*]-1,3,2-dioxaphosphepine to give the desired phosphine–phosphoramidite ligand (**4**).

The new compound exhibited two singlets at 153.48 ppm and 2.97 ppm in the $^{31}P$ NMR spectrum. The Rh complex of the ligand was synthesized by the addition of one equivalent of $[Rh(COD)_2]BF_4$ to the ligand. The $[Rh(COD)(\mathbf{4})]BF_4$ complex showed two doublets of doublets: one at 137.28 ppm was assigned to the amidite phosphorous with P–P coupling of 40.1 Hz and a Rh–P coupling of 242.8 Hz, the other one at 19.19 ppm was assigned to the phosphine phosphorous with Rh–P coupling of 140.5 Hz.

The ligand showed remarkable air and moisture stability. A small sample of compound (**4**) was left in air for one month and only 1% of phosphine oxide was detected according to $^{31}P$ NMR spectroscopy.

**Table 1** Asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid methyl ester with $[Rh(COD)(\mathbf{4})]BF_4$: effect of the solvent and pressure[a]




| Entry | Solvent | Reaction time [h] | Pressure [bar] | *ee* [%] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$[b] | 5.1 | 1 | 98.8 |
| 2 | $CH_2Cl_2$[b] | 1.2 | 5 | 99.0 |
| 3 | MeOH | 2.0 | 5 | 99.9 |
| 4 | MeOH[c] | 20.0 | 1 | 75.0 |
| 5 | EtOAc | 0.4 | 5 | 99.2 |
| 6 | Ethylene carbonate[d,e] | 1.5 | 5 | 99.8 |
| 7 | Propylene carbonate | 2.8 | 5 | 99.2 |
| 8 | Propylene carbonate[d] | 2.9 | 5 | 99.6 |
| 9 | Glycerine carbonate[d,e] | 19.0 (conv. = 64%) | 5 | 72.0 |
| 10 | EtOH (v/v = 96%) | 0.75 | 5 | 99.8 |

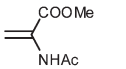
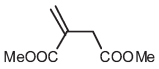
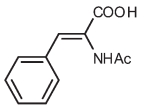
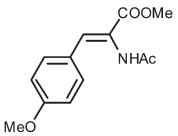
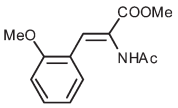
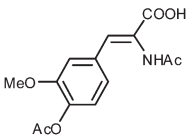
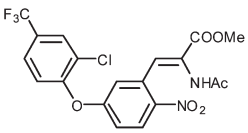
[a] *Reaction conditions*: The catalyst was prepared *in situ*. 0.01 mmol $[Rh(COD)_2]BF_4$ and 0.011 mmol ligand was stirred for 10 minutes in 5 mL solvent. 1.25 mmol substrate was added and pressurized with $H_2$. The reaction was stirred at RT until full conversion. [b] Solvent: 10 mL. [c] Result with MonoPhos.[31] [d] The catalyst was prepared in MeOH. [e] Reaction temperature: 50 °C.

### Homogeneous asymmetric hydrogenation

The new ligand (**4**) was tested in the typical Rh-catalyzed asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid methyl ester (Table 1). All reactions were carried out at room temperature and were stirred and pressurized until full conversion. It quickly became apparent that our ligand provides excellent selectivity at ambient pressure in $CH_2Cl_2$, but deposition of Rh metal was observed during the reaction (entries 1 and 2). By switching to solvents with higher donor number the deposition was eliminated, because solvents having better coordinating properties might protect the complex from reduction if no substrate is present. It is also important to note that the catalyst exhibited the best performance in protic solvents like MeOH and fine spirit (entries 3 and 10). The result achieved with MonoPhos (entry 4) shows that our bidentate phosphorus ligand outperforms its monodentate analogue.

One of the key principles of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign ones. Alkylene carbonates emerged recently as green solvents. The JEFFSOL® carbonates can be used as safe and environmentally friendly solvents replacing the commonly used harsh methylene chloride, acetone, aromatic solvents, and other highly volatile and hazardous solvents. They also have low vapor pressure which allows their facile application at higher temperature. A review on the application of organic carbonates as solvents in catalysis has recently been published.[32]

**Table 2** Asymmetric hydrogenation of some substrates with [Rh(COD)(**4**)]$BF_4$[a]

| Entry | Substrate | Solvent | Reaction time [h] | *ee* [%] |
|---|---|---|---|---|
| 1 |  | Propylene carbonate | 2.2 | 97.7 |
| 2 | | MeOH | 0.3 | 97.9 |
| 3 |  | Propylene carbonate | 3.0 | 99.5 |
| 4 | | —[b] | 9.0 | 98.7 |
| 5 | | MeOH | 1.5 | 98.6 |
| 6 |  | MeOH | 1.8 | 99.5 |
| 7 |  | MeOH | 0.5 | 99.9 |
| 8 |  | MeOH | 0.3 | 99.9 |
| 9 |  | Propylene carbonate | 3.0 | 99.0 |
| 10 | | MeOH | ~7 | 96.7 |
| 11 |  | Propylene carbonate | 0.9 | 98.0 |
| 12 | | MeOH | 0.8 | 97.3 |

[a] *Reaction conditions*: see footnote in Table 1. [b] The catalyst was prepared in MeOH. After evaporation of MeOH, 25 mmol substrate was added to the catalyst. Reaction temperature: 50 °C.

Reactions carried out in propylene carbonate provided excellent *ee*'s (entries 7 and 8). The reaction in pure ethylene carbonate was carried out at 50 °C, but the *ee* remained over 99% (entry 6). This result also indicates that the selectivity of our catalyst is not sensitive to temperature increase. Glycerine carbonate was not found to be a satisfactory solvent (entry 9). Low reactivity and enantioselectivity were obtained due to the low solubility of $H_2$ and/or the high viscosity of this solvent.

We have also investigated the application of the novel catalyst for a variety of substrates. In every case outstanding activities and enantioselectivities (Table 2) were obtained. The catalyst is tolerant for acidic substrates: for example the benchmark substrate (*Z*)-α-acetamidocinnamic acid and the L-DOPA precursor were hydrogenated with enantioselectivities of 99.5% and 99.0%, respectively, at room temperature and only at 5 bar pressure (entries 6, 9 and 10). These results underline the potential and stability of our catalytic system even in acidic reaction conditions. In addition, we were able to eliminate the toxic dichloromethane solvent from the process.

We have also investigated the structural variations on the substrate, and found that substituent on the phenyl group has little or no effect on the enantioselectivity of the reaction. Derivatives with *ortho*- or *para*-OMe electron donating groups resulted in remarkable enantioselectivity (entries 7 and 8).

Our catalyst provided excellent enantioselectivity up to 99.0% in propylene carbonate for the asymmetric hydrogenation of L-DOPA precursor (entry 9). Notably, the DIPAMP[33] (1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane) based catalyst has been used for a long time by Monsanto in the technical production of DOPA (a widely used drug for treating Parkinson's disease). It is interesting to note that enantioselective Rh-catalyzed homogeneous hydrogenation of 3-methoxy-4-acetoxy-(*Z*)-α-acetamidocinnamic acid with [Rh(COD)(*R*,*R*)-DIPAMP]$BF_4$ gave 88.5% enantiomeric excess.[34]

Another important aspect of green chemistry is the development of more effective separation techniques. The workup of propylene carbonate reactions can often be a problem due to its high boiling point (242 °C) and solubility in water. The quick/easy workup of the crude product with less solvent used is more environmentally friendly. In our experiment the product of the asymmetric hydrogenation of L-DOPA precursor could be easily filtered from the reaction mixture at room temperature, washed with ether, dried and then obtained with 71% yield and 99.6% optical purity. This result was achieved without any optimization of the process.

A highly desirable goal of green chemistry is to replace organic solvents in chemical reactions with water. An alternative is to carry out the reaction without any solvent. In our case we were able to carry out the chemical transformation of dimethyl itaconate without any solvent at elevated temperature since our catalyst exhibited no temperature sensitivity. The hydrogenated product was obtained at 50 °C with 98.7% enantioselectivity at a substrate/catalyst molar ratio of 2500 (entry 4).

A biologically active amino acid diphenylether derivative could be readily obtained by the asymmetric hydrogenation of the corresponding dehydroamino acid derivative (entries 11 and 12) with good selectivity in propylene carbonate and in MeOH. Generally, the catalyst gave better performance in propylene carbonate than in MeOH except for methyl acetamido acrylate. In this case the selectivity was approximately the same (entries 1 and 2).

### Heterogeneous asymmetric hydrogenation

An elegant heterogenization method of metal complexes was introduced by Augustine *et al.* using rhodium complexes immobilized on a mesoporous $Al_2O_3$ support with PTA as an anchoring agent.[35] Sheldon *et al.* developed a new aluminium silicate with ideal characteristics for catalyst immobilization, AlTUD-1, as a support for chiral rhodium catalysts used in asymmetric hydrogenation.[36]

First, we anchored our catalyst on the commercially available neutral gamma alumina support ($Al_2O_3^{140}$, $S_{BET}$ = 140 $m^2$ $g^{-1}$) by means of PTA. The catalyst [Rh(COD)(**4**)]/PTA/$Al_2O_3^{140}$ was tested in heterogeneous batch mode (Table 3). The results show that the system continuously lost its catalytic activity during recycling, however, the enantioselectivity remained consistently high, indicating a catalyst decomposition involving the formation of a catalytically inactive oxo-species.

**Table 3** Asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid methyl ester with [Rh(COD)(**4**)]/PTA/$Al_2O_3$[140], batch system[a]

| No. of run | Conv. [%] | *ee* [%] |
|---|---|---|
| 1 | 72.8 | 97.5 |
| 2 | 73.9 | 96.9 |
| 3 | 54.8 | 93.3 |
| 4 | 31.1 | 97.0 |
| 5 | 31.1 | 98.0 |
| 6 | 10.4 | 97.8 |
| 7 | 4.8 | 97.9 |
| 8 | 3.0 | 97.6 |

[a] *Reaction conditions*: [Rh(COD)(**4**)]/PTA/$Al_2O_3$[140] (85 mg) and substrate (274 mg, 1.25 mmol) were stirred in 5 mL $CH_2Cl_2$ under 5 bar of $H_2$ pressure for 72 minutes. The reaction was stopped and after settling of the catalyst the liquid phase was removed. A new charge of substrate in 5 mL $CH_2Cl_2$ was added and the reaction was repeated.

**Table 4** Asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid methyl ester with [Rh(COD)(**4**)]/PTA/$Al_2O_3$[431], flow system[a]

| Time [min] | Conversion [%] | *ee* [%] |
|---|---|---|
| 80 | >99 | 98.8 |
| 130 | >99 | 99.3 |
| 175 | >99 | 99.4 |
| 220 | 97.9 | 99.3 |
| 360 | >99 | 99.0 |
| 740 | 90.3 | 93.1 |

[a] Reaction conditions: The CatCart® contained 164.4 mg [Rh(COD)(**4**)]/PTA/$Al_2O_3$[431] catalyst, solvent EtOAc, pressure 1 bar, substrate concentration 0.05 mol $L^{-1}$, temperature 25 °C, flow rate 0.1 mL $min^{-1}$.

To improve the productivity of the immobilized catalyst, the microstructure of the support was changed from $Al_2O_3$[140] to $Al_2O_3$[431] with a larger surface area.[37] Nitrogen adsorption–desorption isotherms were measured for supports and immobilized complexes (Rh-PTA/$Al_2O_3$), respectively (ESI†). In all cases, these isotherms presented the characteristic form of mesoporous materials. It can be easily remarked that the $N_2$-adsorbed/desorbed volume was higher in the case of pure carrier than in the case of immobilized complexes.

Screening of the heterogenized catalyst [Rh(COD)(**4**)]/PTA/$Al_2O_3$[431] was performed by filling the catalyst in CatCart® cartridges and the reaction carried out using the H-Cube® microfluid reactor (Table 4).[38] This continuous flow system provides safe optimization of the reaction conditions (flow rate, temperature, pressure, solvent, substrate concentration) in a short period of time with only a small amount of catalyst and substrate used. It has been demonstrated that the novel catalyst is applicable in flow based enantioselective hydrogenation and can work continuously for 6 h with over 99% conversion and over 99% enantioselectivity, and another 6 h with over 90% conversion and an average of 97% enantioselectivity.

## Conclusions

The novel phosphine–phosphoramidite ligand (**4**) proved to be highly active in rhodium-catalyzed asymmetric hydrogenation. This ligand exhibits an extraordinary stability towards air and moisture, and tolerance of various hydrogenation conditions, which make this ligand highly practical for general laboratory preparations as well as scale-up operations. Screening of substrates in different solvents showed that enantioselectivities up to >99% can be reached in a range of green solvents like ethylene- and propylene carbonate. We have also demonstrated that propylene carbonate is a viable solvent for asymmetric hydrogenation of dehydroamino acids.

The *in situ* formed [Rh(COD)(**4**)]$BF_4$ complex was immobilized on mesoporous $Al_2O_3$[431] support using PTA as an anchoring agent. A continuous-flow reaction system was applied using a stationary-phase catalyst for the asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid methyl ester. It has been demonstrated that the novel catalyst is applicable in flow-based enantioselective hydrogenation and can work continuously for 6 h with over 99% conversion and with over 99% enantioselectivity, and then another 6 h with over 90% conversion and an average of 97% enantioselectivity.

## Experimental

### (2*S*,4*R*)-2-Isopropylamino-4-sulfatopentane (2)

A solution of (4*R*,6*R*)-4,6-dimethyl-1,3,2-dioxathiane 2,2-dioxide (3.27 g, 19.7 mmol) and isopropylamine (7.5 mL, 88.5 mmol) was stirred in 40 mL of THF for 48 hours meanwhile white precipitate formed. After that the solvent was evaporated and 60 mL of ether was added to the residue. The suspension was stirred for 30 minutes and filtered. The solid was washed two times with ether, dried with azeotropic distillation of toluene. The solvent was evaporated by vacuum to give (2*S*,4*R*)-2-isopropylamino-4-sulfatopentane as a white powder (4.33 g, 98.1%).

$[\alpha]_D^{20} = 0°$ (*c* 1.00 in DMSO), m.p.: 241–242 °C.

Elemental analysis:

Found: C, 42.69; H, 8.31; N, 6.28; S, 14.58. Calc. for $C_8H_{19}NO_4S$: C, 42.65; H, 8.50; N, 6.22; S, 14.23%.

$^1$H NMR (500 MHz, DMSO): $\delta$ = 7.97 (s, 2H, $NH_2^+$), 4.28–4.06 (m, 1H, CH), 3.46–3.13 (m, 2H, CH), 1.71–1.62 (m, 1H, $CH_2$), 1.49–1.41 (m, 1H, $CH_2$), 1.28–0.85 (m, 12H, $CH_3$). $^{13}$C {$^1$H} NMR (75 MHz, DMSO): $\delta$ = 70.99 (s), 49.31 (s), 46.67 (s), 22.59 (s), 19.85 (s), 18.53 (s), 16.80 (s).

### (2*S*,4*S*)-2-Diphenylphosphino-4-isopropylaminopentane (3)

$LiPPh_2$ in 1,4-dioxane (16.6 g, 59.3 mmol) was dissolved in 80 mL of abs. THF under argon atmosphere. (2*S*,4*R*)-2-Isopropylamino-4-sulfatopentane (4.2 g, 18.7 mmol) was added dropwise to the red solution in small portions. The reaction mixture was stirred for 3 hours. The color of the reaction mixture remained red. After evaporation of the solvent, 80 mL of distilled oxygen-free water and 60 mL of ether was added to the residue and the mixture was stirred until the two phases became clear solutions. The pH was then adjusted to 1 with 10% solution of oxygen-free HCl. The phases were then separated and the water phase was washed three times with 30 mL portions of ether. The pH was then set to around 9–10 with dropwise addition of $Na_2CO_3$. The product was then extracted four times with 30 mL portions of ether. After drying over $MgSO_4$ the mixture was

filtered and evaporated. Purification was performed with flash chromatography over silica gel with chloroform–methanol = 4 : 1 eluent to give (2*S*,4*S*)-2-diphenylphosphino-4-isopropylaminopentane as a clear transparent oil (3.40 g, 58.0%). The product was dried with azeotropic distillation of toluene.

$[\alpha]_D^{20} = -76.29°$ (*c* 0.97 in $CH_2Cl_2$).

Elemental analysis:

Found: C, 76.23; H, 8.87; N, 4.39. Calc. for $C_{20}H_{28}NP$: C, 76.64; H, 9.00; N, 4.47%.

$^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 7.52–7.48 (m, 4H, aromatic), 7.32–7.31 (d, 6H, aromatic), 2.98–2.81 (m, 2H, CH), 2.50–2.34 (m, 1H, CH), 1.59–1.43 (m, 1H, $CH_2$), 1.40–1.23 (m, 1H, $CH_2$), 1.14–0.95 (m, 12H, $CH_3$). $^{31}P$ {$^1H$} NMR (121 MHz, $CDCl_3$): $\delta$ = 0.00 (s). $^{13}C$ {$^1H$} NMR (75 MHz, $CDCl_3$): $\delta$ = 137.13 (d, $J$ = 14.89 Hz), 137.13 (d, $J$ = 14.27 Hz), 133.73 (dd, $J$ = 4.96, Hz $J$ = 19.23 Hz), 128.73 (s), 128.34 (t, $J$ = 6.51 Hz), 47.66 (d, $J$ = 12.41 Hz), 45.24 (s), 40.97 (d, $J$ = 16.75 Hz), 27.33 (d, $J$ = 9.92 Hz), 23.34 (d, $J$ = 26.67 Hz), 20.29 (s), 16.32 (d, $J$ = 15.51 Hz).

### *N*-((2*S*,4*S*)-4-(Diphenylphosphino)pentan-2-yl)-*N*-isopropyl-(*S*)-dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepin-4-amine (4)

(2*S*,4*S*)-2-Diphenylphosphino-4-isopropylaminopentane (1.0 g, 3.19 mmol) was dissolved in 20 mL of abs. THF and cooled to 0 °C. BuLi (2.48 mL, 3.51 mmol, 9.8 mg $mL^{-1}$ Li in hexane) was added dropwise. The color of the solution turned to yellow. After stirring at 0 °C (*S*)-chlorodinaphtho[2,1-*d*:1′,2′-*f*]-1,3,2-dioxaphosphepine (1.45 g, 4.15 mmol) in 10 mL of abs. THF was fed to the reaction mixture. Formation of a white precipitate was observed. The mixture was stirred for one hour. The reaction mixture was filtrated through a short pad of silica and was evaporated to give yellow foam. Purification was performed with flash chromatography on silica gel with the n-hexane : ethyl acetate = 20 : 1. Rf.: 0.7 (0.67 g, 33.0%). The pure product is a white solid.

$[\alpha]_D^{20} = 176.12°$ (*c* 1.00 in $CH_2Cl_2$), m.p.: 133–150 °C.

Elemental analysis:

Found: C, 76.55; H, 6.21; N, 2.17. Calc. for $C_{40}H_{39}NO_2P_2$: C, 76.54; H, 6.26; N, 2.23%.

$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.03–7.71 (m, 4H, aromatic), 7.59–7.14 (m, 18H, aromatic), 3.55–3.37 (m, 1H, CH), 3.37–3.23 (m, 1H, CH), 2.41–2.23 (m, 1H, CH), 1.98–1.80 (m, 1H, $CH_2$), 1.77–1.60 (m, 1H, $CH_2$), 1.29 (d, 3H, $CH_3$), 1.07 (dd, 6H, $CH_3$), 0.78 (dd, 3H, $CH_3$). $^{31}P$ {$^1H$} NMR (121 MHz, $CDCl_3$): $\delta$ = 153.48 (s), 2.97 (s). $^{13}C$ {$^1H$} NMR (75 MHz, $CDCl_3$): $\delta$ = 150.14 (d, $J$ = 4.44 Hz), 150.11 (s), 136,94 (d, $J$ = 11.16 Hz), 136.75 (d, $J$ = 12.41 Hz), 133.92 (d, $J$ = 19.23 Hz), 133.44 (d, $J$ = 17.98 Hz), 132.80 (d, $J$ = 8.07 Hz), 131.35 (s), 130.71 (s), 129.96 (d, $J$ = 37.21 Hz), 128.78 (d, $J$ = 9.92 Hz), 128.39 (dd, $J$ = 1.86 Hz, $J$ = 6.82 Hz), 128.21 (s), 127.09 (d, $J$ = 3.72 Hz), 125.90 (d, $J$ = 9.92 Hz), 124.50 (d, $J$ = 25.43 Hz), 124.01 (d, $J$ = 5.58 Hz), 122.38 (d, $J$ = 4.96 Hz), 121.92 (d, $J$ = 2.48 Hz), 46.65 (d, $J$ = 13.02 Hz), 46.43 (d, $J$ = 13.03 Hz), 45.51 (d, $J$ = 6.08 Hz), 27.40 (d, $J$ = 10.88 Hz), 23.94 (d, $J$ = 6.82 Hz), 21.83 (d, $J$ = 10.54 Hz), 15.17 (d, $J$ = 14.26 Hz).

### Asymmetric hydrogenation in flow system

The H-Cube® system is designed for the hydrogenation of a continuous flow of substrate which is flowed through the system by the built in HPLC pump. Pure hydrogen gas is generated by electrolytic water decomposition. The hydrogen gas and a solution of the reactant are mixed, preheated (if needed), and transferred to a disposable catalyst cartridge CatCart® that is preloaded with the required heterogeneous catalysts. The product then flows out of the cartridge and is collected in a vial or flask. The CatCart® system is made up of a stainless steel tube (normal size: 30 × 4 mm) packed with the heterogeneous catalyst. A filter system at either end of the tube allows liquid to pass through the column, but prevents solid particles leaving the cartridge. The columns contained 164.4 mg of [Rh(COD)(**4**)]/PTA/$Al_2O_3$[431]. The instrument works in two modes: in full hydrogen mode a large excess of hydrogen is generated at 1 bar (30 mL $min^{-1}$ hydrogen *vs.* 0.1 mL $min^{-1}$ solution, Table 4) which gives a gas–liquid mixture. In this condition the residence time in the reactor is extremely low (approximately 1 sec at 0.1 mL $min^{-1}$ flow rate) and at the same time the reactor operates with a $H_2$/S/Rh molar ratio of 240/1/360.

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