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Enantioselective hydrogenation catalyzed by highly active rhodium complexes of chiral phosphites with atropisomeric moieties

Ildikó Gergely,[a] Csaba Hegedüs,[b] Henrik Gulyás,[b] Áron Szöllősy,[c] Axel Monsees,[d] Thomas Riermeier[d] and József Bakos[a,*]

[a]*Department of Organic Chemistry, University of Veszprém, H-8201 Veszprém, Hungary*
[b]*Research Group for Petrochemistry, Hungarian Academy of Science, PO Box 158, H-8201 Veszprém, Hungary*
[c]*Department of General and Analytical Chemistry, Technical University of Budapest, H-1521 Budapest, Hungary*
[d]*Degussa AG, Projecthause Catalyse, Industriepark Höchst, Building G830, D-65926 Frankfurt a. M., Germany*

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Abstract—Excellent ee's and extremely high activities are obtained in the rhodium-catalyzed hydrogenation of dimethyl itaconate using simple and readily available H_8-BINOL based monodentate phosphites. The hydrogenation proceeds efficiently even at a substrate concentration of 5.263 mol L^{-1} and at a substrate to catalyst ratio (S/C) of 40,000 to give the product in 95.1% yield with up to 96.9% ee.

Asymmetric catalytic hydrogenation is one of the most efficient and convenient methods for preparing a wide range of enantiomerically pure compounds.[1] The precise control of molecular chirality plays an increasingly important role in chemistry, life science and materials science. High activity, selectivity and stability, readily accessible ligands and enzyme-like stereocontrol are among the characteristic features of an ideal catalyst for practical asymmetric synthesis.[1]

With the reports of Horner[2] and two Monsanto chemists, Knowles and Sabacky,[3] chiral monophosphanes began to be used as chiral modifiers for asymmetric enantioselective hydrogenation. However, shortly thereafter Kagan's group[4] (DIOP) and Knowles et al.[5] (DIPAMP) demonstrated that in the hydrogenation reaction the rhodium complexes of chelating diphosphanes (ee 90%) are superior compared to the corresponding monophosphanes (ee = 3–15%). In view of recent successes with monodentate ligands[6] and with H_8-BINOL based ligands[7] we decided to design new phosphites incorporating these advantageous features. Herein, we report monodentate phosphites as new ligands for the enantioselective hydrogenation of itaconic acid dimethyl ester (Scheme 1) with exceptionally high activity.

The novel ligands **4a** and **4b** were prepared by the reaction of enantiomerically pure (*S*)-2-chloro-5,5′,6,6′,7,7′,8,8′ - octahydrodinaphtho[2,1 - *d*:1′,2′ - *f*][1,3,2]-dioxaphosphepine based on (*S*)-H_8-BINOL (H_8-BINOL = 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol) with the corresponding alcohol.[8] (*S*)-H_8-BINOL can be readily derived from BINOL using the protocol of Cram.[9] For a comparative study, the (*S*)-BINOL (1,1′-bi-2-naphthol) based mono (**3a**, **3b**)[6] and chelating diphosphite analogues ((2*S*,4*S*)-bis-(*S*)-**5** and (2*S*,4*S*)-bis-(*S*)-**6**) have also been synthesized.[10]

The precatalysts were prepared in the usual way by the reaction of phosphites with $[Rh(cod)_2]BF_4$ in CH_2Cl_2 (ligand to Rh molar ratio is generally 2:1). NMR spectroscopic analysis showed that complexes with two coordinated ligands in *cis* positions were formed.[11] The conditions used for the hydrogenation are given in Table 1.[12]

To see if combining H_8-BINOL with chiral and achiral alcohols leads to efficient ligands, the two phosphites **4a**, **4b**, prepared from racemic 1-phenylethanol and isopropanol, respectively, were tested in the Rh-catalyzed hydrogenation of **1**. Reetz and Mehler demonstrated that the chiral binaphthyl unit of monodentate binaphtholphosphites (**3a** and **3b**) determines the enantioselectivity of the reduction,[6] the configuration of the stereogenic carbon of the *sec*-phenethyloxy residue of

* Corresponding author. Tel.: 36-88-422022; fax: 36-88-427492; e-mail: bakos@almos.vein.hu

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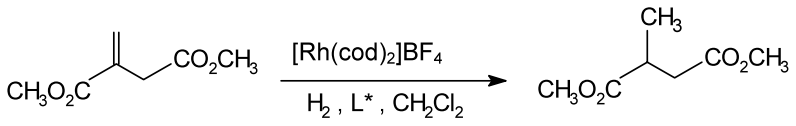

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Scheme 1. Asymmetric catalytic hydrogenation. cod = cycloocta-1,5-diene, L* = chiral ligand.

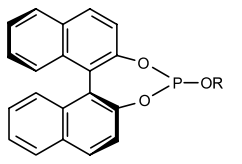
Table 1. Enantioselective Rh-catalyzed hydrogenation of itaconic acid dimethyl ester **1**[a]

Entry	Ligand	Time (min)	$p(H_2)$ (bar)	P/Rh ratio	Ee[b] (%)
1	**3a**	180	1	2	98.1 (*S*)
2	**3a**	15	20	2	97.6 (*S*)
3	**4a**	165	1	2	98.3 (*S*)
4	**4a**	5	20	2	97.6 (*S*)
5	**4a**	4	60	2	94.2 (*S*)
6	**3b**	135	1	2	98.9 (*S*)
7	**3b**	20	20	1.2	96.3 (*S*)
8	**4b**	120	1	2	98.7 (*S*)
9	**4b**	15	20	1	96.2 (*S*)
10	**4b**	15	20	2	96.9 (*S*)
11	**5**	30	20	2.2	59.7 (*R*)
12	**6**	10	20	2.2	88.5 (*R*)

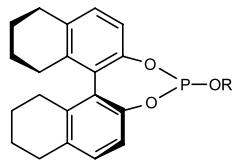
[a] *Reaction conditions*: solvent CH_2Cl_2; 23°C; *c* (substrate) = 0.467 mol L^{-1}; S/C = 1000; catalyst preparation see text; 100% conversion was observed.

[b] The enantiomeric excess of the product was determined by GC analysis of the distilled product (Hewlett–Packard HP 4890 gas chromatograph, split/splitless injector, β-DEX 225, 30 m, internal diameter 0.25 mm, film thickness 0.25 μm, carrier gas: 100 kPa nitrogen, FID detector; the retention times of the enantiomers are 33.3 min (*S*), 36.9 min (*R*)). Absolute configuration was determined by comparison with the known sign of specific rotation.

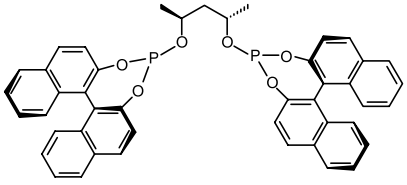
3a does not play any role, we therefore chose to use racemic alcohols. Under otherwise identical conditions, both catalytic systems give excellent ee values. The H_8-BINOL-based catalysts have higher catalytic activity than the BINOL-based systems. Hydrogen pressure had only a slight effect on the enantioselectivity of the reaction, but a profound effect on the reaction rate. The ee's of 98.1–98.9% (entries 1, 3, 6, and 8) were obtained at 1 bar of H_2, but the values decrease to 97.6% (compound **3a**), 97.6% (compound **4a**), 96.3% (compound **3b**), 96.9% (compound **4b**) at 20 bar.



3a R = CH(CH3)Ph
3b R = CH(CH3)2



4a R = CH(CH3)Ph
4b R = CH(CH3)2



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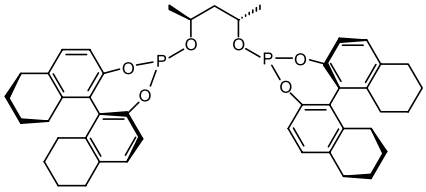

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Table 2. Enantioselective Rh-catalyzed hydrogenation of itaconic acid dimethyl ester **1** at low catalyst loading[a]

Entry	Ligand	S/C	Conv. (%)	Ee (%)
1	**4a**	10,000	100	97.7 (*S*)
2	**4a**	20,000	91.9	98.5 (*S*)
3	**4a**	40,000	58.9	95.9 (*S*)
4	**4b**	10,000	98.2	96.8 (*S*)
5	**4b**	20,000	98.2	96.2 (*S*)
6	**4b**	40,000	72.9	95.5 (*S*)

[a] *Reaction conditions*: solvent CH_2Cl_2; 23°C; $p(H_2)=20$ bar, P/Rh ratio is 2, c (substrate) = 0.467 mol L^{-1}; reaction time is 15 min; for other experimental conditions, see footnotes to Table 1.

An interesting point to note is that high selectivity for the (*S*)-product might be favored by conditions in which the system is starved of hydrogen, and hence working in a diffusion limited system could be beneficial.[13]

When **6**, a partially hydrogenated analogue of **5** was used as a bisphosphite ligand for the catalyst precursor, the enantioselectivity was distinctly higher with **6** than with **5** (Table 1, entries 11 and 12). The lower enantiomeric purities and inverse (*R*) configuration of the product induced by bidentate ligands demonstrate that the mono- and diphosphite systems differ considerably.

While most of the hydrogenation reactions are performed in the presence of 1 mol% of catalyst, use of **4a** and **4b** allows hydrogenation to be carried out at low catalyst loading (0.005 mol%) without observing a negative effect on the yield and selectivity (Table 2). Particularly noteworthy is that, **4a** and **4b** with a substrate:rhodium ratio of 20,000, still afford almost complete conversions (91.9 and 98.2%) and 98.5 and 96.2% ee, respectively, in 15 min under 20 bar pressure.

For practical synthesis, a solvent free system is the ideal process in terms of productivity, reaction volume and environmental safety.[14] However, asymmetric catalytic processes are usually highly sensitive to both solvent and substrate concentration effects. Our previous findings prompted us to further optimize our catalytic system by decreasing the amount of solvent, i.e. by increasing the concentration of the substrate (Table 3). The hydrogenation proceeded efficiently even at substrate concentrations of 4.166 and 5.263 mol L^{-1} to give the product in 94.9 and 95.1% conversions, respectively, with up to 96.9% ee.

The effectiveness of these catalysts is manifested by the high turnover frequencies (TOF). For example, with a substrate:catalyst ratio of 40,000:1 a turnover frequency (calculated for the whole reaction) of higher than 100,000 h^{-1} was obtained (Table 3, entry 3). Finally, **4b** in solvent free conditions at a substrate:catalyst ratio (S/C) of 20,000 catalyzes the hydrogenation of itaconic acid dimethyl ester under 20 bar of H_2 and 23°C to afford the hydrogenated product in 95.4 ee and 91% conversion.

It was reported that Ir(I)- and Ru(II)-complexes of H_8-BINAP served as more effective catalyst precursors for the asymmetric hydrogenation of some substrates than did the analogous complexes of BINAP.[15] Furthermore, the Pd(II) complex of (*R*,*S*)-H_8-BINAPHOS is a more active catalyst compared to (*R*,*S*)-BINAPHOS in the copolymerization of propene with carbon monoxide.[16] The dihedral angles in these structures suggest that ligands having an H_8-BINOL-based backbone possess quite different axial flexibility, however, in our case the seven-membered dioxaphosphepine ring hinders this flexibility. Unfortunately, suitable crystals of the free ligands or their rhodium complexes for X-ray analysis could not be obtained.

In conclusion, our catalytic system provides attractive features: (i) the chemicals are cheap and easily available; (ii) unusually high activity is maintained when the amount of catalyst is reduced; (iii) the reaction is environmentally benign and energy-saving because of the high substrate concentration or solvent free conditions; and (iv) exceptionally low catalyst loading (0.1–0.0025 mol%) is sufficient to achieve high yield and enantiomeric purity of the product. We anticipate that this catalyst system will find use in an extensive array of applications.

Acknowledgements

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Table 3. Enantioselective Rh-catalyzed hydrogenation of itaconic acid dimethyl ester **1** with low catalyst loading and with high concentration of substrate[a]

Entry	Ligand	S/C	c (S) (mol L^{-1})	Time (min)	Conv. (%)	Ee (%)
1	**4b**	20,000	0.877	20	100	96.5 (*S*)
2	**4b**	20,000	4.166	20	94.9	96.0 (*S*)
3	**4b**	40,000	5.263	20	95.1	96.9 (*S*)
4	**4b**	80,000	6.060	60	20.9	83.1 (*S*)

[a] *Reaction conditions*: solvent CH_2Cl_2; 23°C; $p(H_2)=20$ bar, P/Rh ratio is 2; for other experimental conditions, see footnotes to Table 1.

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8. **(*R*,*S*)-(*S*)-2-(1-Phenyl)ethoxy-5,5′,6,6′,7,7′,8,8′-octahydrodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine, 4a (mixture of two diastereomers)**: $^{31}P\{^1H\}$ NMR (202.45 MHz, $CDCl_3$): δ 139.30 (s), 143.10 (s). ^1H NMR (500.13 MHz, $CDCl_3$): δ 1.62 (m, 4H; CH_2), 1.64 (d, $^3J(H,H)=6.3$ Hz, 3H; CH_3), 1.65 (d, $^3J(H,H)=6.3$ Hz, 3H; CH_3), 1.83 (m, 12H; CH_2), 2.34 (m, 4H; CH_2), 2.71 (m, 4H; CH_2), 2.86 (m, 8H; CH_2), 5.37 (m, 2H; CH), 6.37 (d, $^3J(H,H)=8.1$ Hz, 1H; aromatic proton), 6.76 (d, $^3J(H,H)=8.1$ Hz, 1H; aromatic proton), 6.95 (d, $^3J(H,H)=8.1$ Hz, 1H; aromatic proton), 7.01 (d, $^3J(H,H)=8.1$ Hz, 1H; aromatic proton), 7.05 (d, $^3J(H,H)=6.9$ Hz, 1H; aromatic proton), 7.06 (d, $^3J(H,H)=6.9$ Hz, 1H; aromatic proton), 7.12 (d, $^3J(H,H)=8.1$ Hz, 2H; aromatic protons), 7.25–7.45 (m, 10H; Ph-protons). $^{13}C\{^1H\}$ NMR (125.75 MHz, $CDCl_3$): δ 22.91 (s, 2 CH_2 overlapped), 22.99 (s, CH_2), 23.02 (s, CH_2), 23.09 (s, 2 CH_2 overlapped), 23.18 (s, CH_2), 23.20 (s, CH_2), 25.44 (d, $^3J(P,C)=3.6$ Hz, CH_3), 26.13 (d, $^3J(P,C)=3.6$ Hz, CH_3), 28.17 (s, CH_2), 28.20 (s, CH_2 overlapped), 28.23 (s, CH_2), 29.60 (s, 2 CH_2 overlapped), 29.63 (s, CH_2), 29.67 (s, CH_2), 73.82 (d, $^2J(P,C)=13.3$ Hz, CH), 74.24 (d, $^2J(P,C)=19.4$ Hz, CH), 119–147 (aromatic carbons).
(*S*)-2-(1-Methyl)ethoxy-5,5′,6,6′,7,7′,8,8′-octahydrodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine, 4b: mp 94–95°C; $[\alpha]_D^{20}=232.8$ (*c* 1.16, CH_2Cl_2). $^{31}P\{^1H\}$ NMR (202.45 MHz, $CDCl_3$): δ 142.40 (s). ^1H NMR (300.15 MHz, $CDCl_3$): δ 1.28 (d, $^3J(H,H)=5.7$ Hz, 3H; CH_3), 1.32 (d, $^3J(H,H)=6.0$ Hz, 3H; CH_3), 1.55 (m, 2H; CH_2), 1.77 (m, 6H; CH_2), 2.25 (m, 2H; CH_2), 2.64 (m, 2H; CH_2),), 2.79 (m, 4H; CH_2),), 4.47 (m, 1H; CH) 6.84 (d, $^3J(H,H)=8.4$ Hz, 1H; aromatic proton), 6.99 (d, $^3J(H,H)=7.7$ Hz, 1H; aromatic proton), 7.01 (d, $^3J(H,H)=7.7$ Hz, 1H; aromatic proton), 7.06 (d, $^3J(H,H)=8.4$ Hz, 1H; aromatic proton). $^{13}C\{^1H\}$ NMR (75.43 MHz, $CDCl_3$): δ 22.40 (s, CH_2), 22.46 (s, CH_2), 22.58 (s, CH_2), 22.66 (s, CH_2), 24.41 (d, $^3J(P,C)=3.4$ Hz, CH_3), 24.56 (d, $^3J(P,C)=3.5$ Hz, CH_3), 27.71 (s, 2 CH_2 overlapped), 29.10 (s, CH_2), 29.15 (s, CH_2), 68.81 (d, $^2J(P,C)=17.8$ Hz, CH), 118.62 (s), 118.78 (d, $J(P,C)=2.3$ Hz), 127.88 (d, $J(P,C)=2.3$ Hz), 128.84 (s), 129.20 (s), 129.36 (d, $J(P,C)=4.6$ Hz), 133.55 (s), 134.46 (s), 137.42 (s), 138.18 (d, $J(P,C)=2.3$ Hz, 1C), 145.99 (s), 146.51 (s). MS (ESI, m/z) 357 [$M-H^-$].
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11. $[Rh(cod)_2]BF_4$ with **4b** (^{31}P NMR (300 MHz, CD_2Cl_2, 25°C): δ 120.0 ppm ($^1J(P,Rh)=256.5$ Hz).
12. **Typical procedure for catalytic asymmetric hydrogenation**: Reactions were carried out in a 20 ml stainless steel autoclave. The catalysts were made in situ by mixing phosphite **4b** (3.8 mg, 0.01 mmol) with $[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) in CH_2Cl_2 (10 mL) under argon. The solution was stirred for 15 min and then the substrate (0.7 mL, 5 mmol) was added. The mixture was transferred into the autoclave under an argon atmosphere. The autoclave was pressurized with H_2 and then shaken at a frequency of 180/min, 75° from the upright position, with horizontal amplitude of 3 cm. The reaction was monitored by the change in hydrogen pressure.
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