Highly Enantioselective Rhodium-Catalyzed Hydrogenation with Monodentate Ligands

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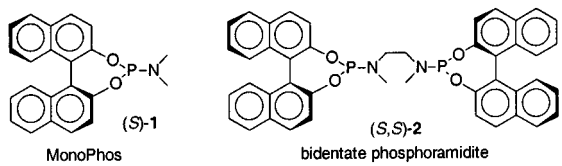
The homogeneous enantioselective hydrogenation of functionalized prochiral olefins is one of the most frequently studied and most efficient transition metal-catalyzed reactions.[1] In the first reports[2] using chiral Wilkinson type catalysts, low enantiomeric excesses (ee's) were obtained using monodentate phosphines as ligands. All attempts to develop monodentate ligands which would afford high ee's in this reaction met with limited success, the best result being reached with CAMP, already published in 1972, giving ee's up to 90% in the hydrogenation of dehydroamino acids.[3]

Although new monodentate phosphorus ligands[4] play a significant role in other transition metal-catalyzed reactions, highly enantioselective hydrogenations are exclusively based on bidentate phosphorus ligands.[1] Starting with Kagan's diop[5] a large number of bidentate ligands with excellent selectivities was designed.[6] Among the most successful are DIPAMP,[7] which gives superior results compared to its monodentate analogue PAMP, the frequently used BINAP ligand,[8] the ferrocenyl-based ligands[9] and the DuPHOS, BPE, and FerroTANE ligands, the latter showing extremely high enantioselectivities and broad scope.[6d,10]

To date, not only phosphines (phosphanes) are used but also bidentate aminophosphines,[11] phosphites,[12] phosphinites,[13] phosphonites,[14] and hybrid ligands such as phosphine−phosphite,[15] aminophosphine−phosphinite,[16] and phosphine−phosphonite,[17] whereas very recently phosphine−phosphoramidite[18] and phosphonite−phosphite[19] ligands were reported.

It is assumed that the use of bidentate ligands results in rigidity in the catalyst which leads to more effective chiral induction.[6a] A similar conclusion has been drawn from the general trend of decreasing enantioselectivity with increasing conformational flexibility of the bidentate ligand.[20] This does not, however, preclude the possibility that rhodium catalysts based on monodentate ligands could show the same high selectivity, especially when the two ligands on rhodium strongly restrict each other's conformational freedom. Encouraging is a recent report by Pringle and co-workers on a monodentate phosphonite ligand which leads to 92% ee at 73% conversion in the rhodium-catalyzed hydrogenation of methyl 2-acetamido acrylate.[21]



Herein we report monodentate phosphoramidites as new ligands for the enantioselective rhodium-catalyzed hydrogenation of olefins with unprecedented high ee's up to 99.8%.

Phosphoramidite ligands have not been used in asymmetric hydrogenation[22] but showed excellent enantioselectivities in copper-catalyzed dialkylzinc additions to enones.[23] With $Rh(COD)_2$-BF_4 as the catalyst precursor and monodentate ligand (*S*)-**1**[24] (2 equiv with respect to rhodium)[25,26] we obtained quantitative conversion under ambient conditions (rt, 1 bar H_2, 20 h) and a

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(24) Easily prepared in one step from (*S*)-(−)-1,1′-bi-2-naphthol and hexamethylphosphorous triamide, see: Hulst, R.; De Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699. We labeled this ligand MonoPhos (*Mono*dentate *Phos*phoramidite).

(25) The optimal ligand-to-rhodium ratio in the reactions appears to be 2:1. With less than two equiv of **1**, rhodium black is formed rapidly, whereas with 3 equiv or more no reaction occurs.

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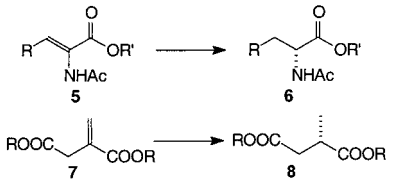
Table 1. Solvent Optimization in the Rhodium-Catalyzed Hydrogenation of Methyl 2-Acetamido Cinnamate[a]

solvent	% ee[b]	conf.[b]
CH_2Cl_2	95	*R*
$ClCH_2CH_2Cl$	89	*R*
MeOH	75	*R*
$CH_3(CH_2)_3OCH_2CH_2OH$	77	*R*
THF	93	*R*
Acetone	92	*R*
EtOAc	93	*R*
MeOAc	95[c]	*R*
toluene	93[c]	*R*

[a] The reaction was performed at room temperature under ambient H_2 pressure for 20 h [substrate (0.2 mmol, 0.04 M):$Rh(COD)_2BF_4$: ligand (*S*)-**1** = 1:0.05:0.11], 100% conversion was observed unless mentioned otherwise. [b] See Supporting Information. [c] Due to poor solubility of the catalyst the reaction was very slow and did not go to completion.

Table 2. Asymmetric Hydrogenation of Dehydroamino Acid and Itaconic Acid Derivatives[a]

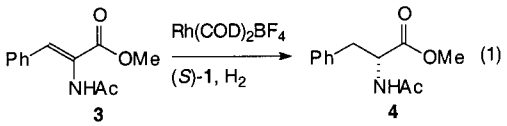


substrate	solvent	% ee[b] 0 °C	% ee[b] 25 °C	conf.[b]
5: R = H, R′ = Me	CH_2Cl_2		99	*R*
5: R = H, R′ = Me	EtOAc	99.8	99.6	*R*
5: R = Ph, R′ = Me	CH_2Cl_2	97.6	95	*R*
5: R = Ph, R′ = Me	EtOAc	98.4	93.2	*R*
5: R = *p*-OAc-*m*-OMePh, R′ = Me	CH_2Cl_2	96.3	95.1	*R*
5: R = *p*-OAc-*m*-OMePh, R′ = Me	EtOAc	98.7		*R*
5: R = H, R′ = H[c]	EtOAc		98.7	*R*
5: R = Ph, R′ = H[c]	CH_2Cl_2		80.5	*R*
5: R = Ph, R′ = H[c]	EtOAc		97.1	*R*
7: R = Me	CH_2Cl_2	94.4	87	*S*
7: R = H[c]	CH_2Cl_2		96.6	*S*
7: R = H[c]	EtOAc		96	*S*

[a] For conditions, see Table 1, 100% conversion was observed in all cases. [b] See Supporting Information. [c] For ee determination, products were converted into their corresponding methyl esters.

reasonable ee (75%) in the hydrogenation of methyl 2-acetamido cinnamate (**3**) in methanol (Table 1).[27]

Screening of solvents led to the unexpected finding that both rate and enantioselectivity are much improved in nonprotic solvents, with CH_2Cl_2 and EtOAc being the solvents of choice. In CH_2Cl_2 the hydrogenation of **3** was complete in 4 h and gave **4** in 95% ee.



The hydrogenation of dehydroamino acid and itaconic acid derivatives was examined in CH_2Cl_2 and EtOAc under ambient pressure at room temperature or 0 °C (Table 2). Optimum ee's are obtained in EtOAc as solvent at 0 °C without prehydrogenation. By varying the substrate it is shown that quantitative conversions and high ee's are found for the recognized benchmark substrates, with excellent selectivities for the acids as well as the corresponding methyl esters (Table 2). Remarkable is the ee of 99.8% obtained in the hydrogenation of methyl 2-acetamido acrylate (**5**, R = H, R′ = Me). These results counter the commonly accepted rule that bidentate ligands are a *conditio sine qua non* for high ee's in this reaction type. For comparison, bidentate (*S,S*)-**2** was also tested in the hydrogenation of **3**. In CH_2Cl_2 at room temperature 72% ee was observed in a slow reaction (56% conversion after 24 h).

Table 3. Asymmetric Hydrogenation with Low Catalyst Loading and Elevated Pressure[a]

substrate	solvent	time (min)	% ee
5: R = H, R′ = Me	EtOAc	10	97
5: R = Ph, R′ = Me	CH_2Cl_2	40	95
5: R = Ph, R′ = Me[b]	EtOAc	4	97
5: R = *p*-OAc-*m*-OMePh, R′ = Me	EtOAc	c	96.6

[a] The reaction was performed at room temperature using 5 bar of H_2 [substrate (0.8 mmol, 0.04M):$Rh(COD)_2BF_4$:ligand (*S*)-**1** = 1:0.005: 0.011], 100% conversion was observed unless mentioned otherwise.[b] rt, 60 bar H_2, $Rh(NBD)_2BF_4$. [c] 69% conversion after 60 min, 100% after 16 h.

High pressures accelerate the hydrogenation reaction, but with a number of bidentate ligands a sharp decrease in ee is encountered.[6] Hydrogenation experiments were performed at 5 bar of H_2 pressure with a decreased amount of catalyst (0.5 mol %), showing only slight differences in ee compared to the hydrogenation under ambient pressure (Table 3). In addition the hydrogenation of **3** was carried out at a pressure of 60 bar (0.9 mol % catalyst)[28] in EtOAc giving a very fast reaction (100% conversion in 4 min) with a slight increase in enantioselectivity (97% ee).

In conclusion, excellent ee's are obtained in the rhodium-catalyzed hydrogenation using a simple and readily available monodentate phosphoramidite chiral ligand. Notable features are the levels of enantioselectivity (>99%) reached, comparable with those of bidentate ligands, and the very fast and enantioselective hydrogenation under high pressure with only negligible effects on the levels of stereocontrol.

The easy preparation of ligand **1** from commercially available starting materials will strongly reduce catalyst costs, thus greatly enhancing prospects of industrial application. Extension of the scope of this reaction and mechanistic studies are currently under investigation.

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Supporting Information Available: Experimental and chromatographic details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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(26) Preliminary semiempirical calculations (PM3) on an anticipated rhodium complex containing two ligands (*S*)-**1** and a substrate molecule show favorable conformations which correspond with the observations of Pringle et al. cf. ref 21. The least stable diastereomer leads to the main product in accordance with the Halpern mechanism, cf. Halpern, J. *Science* **1982**, *217*, 401.

(27) Phosphoramidites, such as **1**, are stable in protic solvents.

(28) $Rh(NBD)_2BF_4$ was used as the catalyst precursor.

(29) After submission of this manuscript Reetz et al. reported on monodentate phosphonite ligands in rhodium-catalyzed enantioselective hydrogenation resulting in 94% ee; Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333