Asymmetric Catalysis

Achiral Ligands Dramatically Enhance Rate and Enantioselectivity in the Rh/Phosphoramidite-Catalyzed Hydrogenation of α,β-Disubstituted Unsaturated Acids**

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In 2000, three research groups demonstrated that the widely held view that chiral bidentate ligands are necessary to achieve high enantioselectivity in rhodium-catalyzed hydrogenations needs revision. Monodentate phosphonites,[1a] phosphites[1b] and phosphoramidites[1c] proved to be highly versatile ligands for this important transformation and afforded excellent enantioselectivities for a broad range of substrates.

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Recently it has been shown that mixtures of chiral monodentate ligands improve the enantioselectivity and reactivity in several cases.[2] This new strategy has been employed in rhodium-catalyzed asymmetric hydrogenations[2,3] and in rhodium-catalyzed additions of boronic acid.[4] By using this mixed-ligand approach and exploiting the fact that the structure of monodentate ligands can be varied easily enables a large number of different catalytic complexes to be screened for a variety of reactions. Reetz and co-workers have also introduced a variation of this mixed-ligand approach using a combination of chiral and achiral ligands.[3a] So far, however, beneficial influences observed for mixed-ligand systems are limited to a mixture of two chiral monodentate ligands.

Herein, we report a mixed-ligand approach in which a combination of a chiral monodentate phosphoramidite and an achiral monodentate phosphine ligand gives for the first time drastic improvement resulting in high, and in some cases unprecedented, enantioselectivities compared to known bidentate ligands and (combinations of) chiral monodentate ligands in the rhodium-catalyzed hydrogenation of disubstituted acrylic acids.

Our efforts focused on chiral dihydrocinnamic acid derivatives, which are key intermediates in the synthesis of several bioactive compounds, including renin inhibitors,[5] γ-secretase inhibitors,[6] enkephalinase inhibitors,[7] endothelin receptor antagonists,[8] and opioid antagonists.[9]

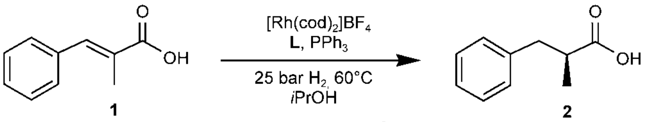
An initial screening of several mixtures of monodentate phosphoramidites and other phosphorus ligands in the rhodium-catalyzed asymmetric hydrogenation of α-methylcinnamic acid (**1**) showed that the heterocombination of a chiral phosphoramidite with an achiral triphenylphosphine gave a dramatic increase in conversion and in enantioselectivity, compared to the corresponding homocomplexes (Table 1).

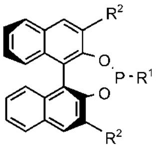
For example the use of **L1c** in combination with triphenylphosphine resulted in an enhancement of the conversion from 76 to 100% and the *ee* value from 0 to 63% (entries 5 and 6). It was observed that phosphoramidites based on 3,3′-dimethyl-2,2′-dihydroxy-1,1′-binaphthyl (3,3′-dimethylbinol) gave distinctly higher *ee* values than the phosphoramidites based on binol (entries 1–8 versus 9–16, Table 1). Piperidine-based phosphoramidite **L2c**[10] further improved the enantioselectivities. The addition of triphenylphosphine in the presence of the catalyst based on **L2c** resulted in a remarkable increase in the *ee* value from 2 to 85% (entries 13 and 14).

A screening of different phosphines was performed after further optimization of the solvent, temperature, pressure, and ligand ratio.[11] A variety of achiral alkyl phosphines and substituted aryl phosphines were tested in the rhodium-catalyzed asymmetric hydrogenation of α-methylcinnamic acid (**1**) using **L2c** (Table 2).

Substitution at the *ortho* position of triphenylphosphine increased the *ee* value significantly (entries 2 and 3), whereas substitution at the *meta* or *para* position had hardly any influence on the enantioselectivity (compare entries 2, 4, 5, 8,

Table 1: Screening of phosphoramidites in the rhodium-catalyzed asymmetric hydrogenation of α-methylcinnamic acid (**1**)[a,b]





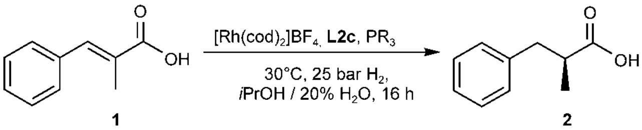
L1a $R^1 = NMe_2$, $R^2 = H$
L1b R^1 = morpholine, $R^2 = H$
L1c R^1 = piperidine, $R^2 = H$
L1d R^1 = (*R*)-α-methylbenzylamine, $R^2 = H$

L2a $R^1 = NMe_2$, $R^2 = Me$
L2b R^1 = morpholine, $R^2 = Me$
L2c R^1 = piperidine, $R^2 = Me$
L2d R^1 = pyrrolidine, $R^2 = Me$

Entry	Ligand	Conversion [%]	*ee*[c,d] [%]
1	**L1a**	43	8
2	**L1a** + PPh_3	100	43
3	**L1b**	72	0
4	**L1b** + PPh_3	100	55
5	**L1c**	76	0
6	**L1c** + PPh_3	100	63
7	**L1d**	91	0
8	**L1d** + PPh_3	100	37
9	**L2a**	91	10
10	**L2a** + PPh_3	100	80
11	**L2b**	82	3
12	**L2b** + PPh_3	100	80
13	**L2c**	81	2
14	**L2c** + PPh_3	100	85
15	**L2d**	86	16
16	**L2d** + PPh_3	100	76

[a] Reaction conditions: 1 mmol substrate in 4 mL solvent with 0.01 mmol $[Rh(cod)_2]BF_4$ (cod = cycloocta-1,5-diene), 0.02 mmol phosphoramidite and 0.01 mmol PPh_3. [b] Reactions were carried out for 5 h. [c] *ee* values were determined by GC on a chiral stationary phase (see Supporting Information). [d] In all cases the *R* enantiomer of the ligand gave the *S* enantiomer of the product.

Table 2: Screening of achiral phosphines in the rhodium-catalyzed asymmetric hydrogenation of α-methylcinnamic acid (**1**)[a,b]

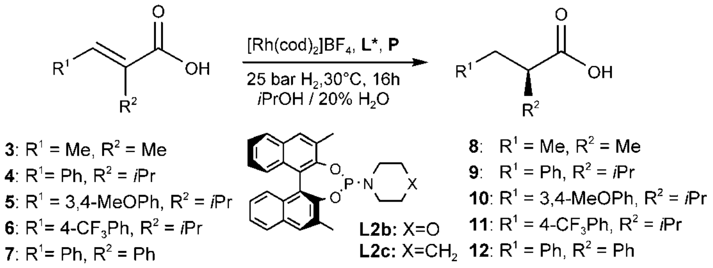


Entry	R	*ee*[c,d] [%]	TOF [mol mol^{-1} h^{-1}]
1	–	16[e]	2
2	Ph (**P1**)	88	46
3	*o*-tolyl (**P2**)	97	33
4	*m*-tolyl (**P3**)	87	69
5	*p*-tolyl (**P4**)	86	61
6	xylyl (**P5**)	89	92
7	mesityl (**P6**)	33[f]	3
8	*m*-ClPh (**P7**)	89	46
9	*p*-ClPh (**P8**)	90	18
10	cyclohexyl (**P9**)	87	28
11	*n*-butyl (**P10**)	67	17
12	*tert*-butyl (**P11**)	13[g]	2

[a] Reaction conditions: 1 mmol substrate in 4 mL solvent with 0.01 mmol $[Rh(cod)_2]BF_4$, 0.02 mmol phosphoramidite and 0.01 mmol PR_3. [b] Reactions were carried out for 16 h. [c] *ee* values were determined by GC on a chiral stationary phase (see Supporting Information), full conversion. [d] In all cases the *R* enantiomer of the ligand gave the *S* enantiomer of the product. [e] 34% conversion. [f] 55% conversion. [g] 39% conversion.

and 9). Linear or branched alkyl phosphines resulted in a decrease in the rate and enantioselectivity compared to tricyclohexylphosphine **P9** (entries 10–12). Electron-donating or -withdrawing substituents on the aryl phosphines had no influence on the *ee* value (compare entries 2 with 4 and 5 as well as 8 and 9). While reactions were in general complete after 2 h, incomplete conversions were obtained with the sterically hindered phosphines **P6** and **P11** after 16 h (entries 7 and 12). In these cases, not only did the rate of the hydrogenations decrease, but the enantioselectivities also dropped dramatically.

Table 3: Rhodium-catalyzed asymmetric hydrogenation of substituted acrylic acids[a],[b]



Entry	Substrate	Product	Ligand	Phosphine	*ee*[c,d] [%]
1	**3**	**8**	**L2b**	**P3**	87
2	**4**	**9**	**L2c**	**P2**	99[e]
3	**5**	**10**	**L2c**	**P1**	92
4	**6**	**11**	**L2c**	**P3**	95
5[f]	**7**	**12**	**L2c**	**P2**	95

[a] Reaction conditions: 1 mmol substrate in 4 mL solvent with 0.01 mmol [Rh(cod)$_2$]BF$_4$, 0.02 mmol phosphoramidite and 0.01 mmol PPh$_3$. [b] Reactions were carried out for 16 h. [c] *ee* values were determined by GC or HPLC on chiral stationary phases, full conversion was obtained unless indicated otherwise. [d] In all cases the *S* enantiomer of the ligand gave the *S* enantiomer of the product.[15] [e] Conversion 98%. [f] Reaction was performed at 60°C.

Next the hydrogenation of a number of disubstituted acrylic acids was studied (Table 3). In all cases, full conversion of the substrates was obtained with high to excellent *ee* values. The enantioselectivity is higher when R^1 is an aromatic group than when R^1 is an alkyl group, as in tiglic acid (**3**, compare entry 3 of Table 2 with entry 1 of Table 3). Electron-donating as well as electron-withdrawing substituents at the aromatic moiety had little effect on the enantioselectivity (entry 3 versus 4, Table 3). The size of R^2 also has little influence on the enantioselectivities. Enantiomeric excesses of $\geq 97\%$ for **2** and **9** could be obtained by fine-tuning of the phosphine–phosphoramidite combination (entry 3 of Table 2 and entry 2 of Table 3).

On the basis of preliminary NMR experiments it can be concluded that the formation of a heterocomplex comprising one chiral phosphoramidite and one achiral phosphine bound to the Rh center is the predominant factor for the remarkable selectivity enhancement and high activity. The formation of a homocomplex comprising two achiral phosphines bound to the Rh center causes a non-asymmetric catalytic reaction. Using a 2:1 ratio of phosphoramidite:phosphine suppresses the formation of the latter homocomplex.

The enantioselectivities obtained here for products **2** and **12** exceed or are comparable to reported values for rhodium-catalyzed and ruthenium-catalyzed hydrogenations using chiral bidentate ligands.[5a,12,13] With the exception of five Ru complexes based on bidentate phosphine ligands, which hydrogenate substrate **3** with $\geq 95\%$ *ee*,[12f,13b,13c,14] the present system belongs to the most selective so far reported.

In conclusion, a new catalytic system, based on a mixed-ligand approach, has been developed for the rhodium-catalyzed asymmetric hydrogenation of cinnamic acid derivatives with *ee* values up to 99%. Easy variation of the chiral and achiral monodentate ligands makes it possible to screen a variety of catalytic systems in a short time. It has been shown for the first time that a catalyst complex based on a heterocombination of a chiral and an achiral monodentate ligand gives dramatically higher enantioselectivity than any of the corresponding homocomplexes.

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[15] The absolute configuration of **11** was confirmed by X-ray analysis of the corresponding α-methylbenzylamine derivative. The absolute configurations of **9** and **10** were assigned by analogy (see Supporting Information).