Asymmetric Catalysis with Chiral Phosphane/Phosphoramidite Ligands Derived from Quinoline (QUINAPHOS)**

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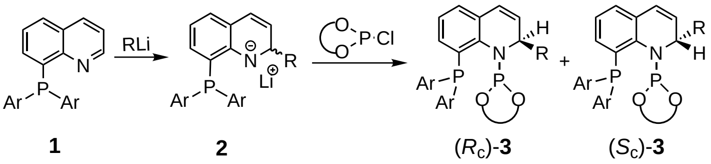
Dedicated to Professor Dirk Walther
on the occasion of his 60th birthday

The use of chiral transition metal complexes as homogeneous catalysts is a well-established and highly attractive strategy for synthesis of optically active products.[1] Chiral bidentate phosphorus compounds are highly efficient ligands for many important reactions involving late transition metal catalysts.[2, 3] Consequently, the quest for new efficient ligand systems is a major challenge in catalysis research. Ideally, such ligands should be accessible in both enantiomeric forms, readily available from simple starting materials, and applicable to a broad spectrum of catalytic reactions.

Here we introduce a new family of bidentate chiral ligands which contain 2-alkyl-1,2-dihydroquinoline as a simple, but highly effective chiral backbone. The ligands have two different phosphorus donor sites connected to positions 1 and 8 of the heterocycle backbone. As shown in Scheme 1, we initially focused on phosphane/phosphoramidite ligands, but other substitution patterns can be envisaged. The first example of this series, *n*Bu-QUINAPHOS (**3a**),[4–6] is unique in that it is among the most efficient ligands for rhodium-catalyzed hydrogenation as well as rhodium-catalyzed hydroformylation. The asymmetric induction is mainly determined by the chiral center in the 2-position of the quinoline framework, which is therefore an ideal starting point for further optimization of the ligand structure.



Scheme 1.

The new ligands **3a–d** are synthesized in a one-pot-procedure from readily available 8-bisarylphosphanylquinolines **1**[7] by nucleophilic addition of an organometallic reagent[8] and direct quenching of the resulting 1,2-dihydroquinoline salt **2** with phosphorochloridites[9, 12] (Scheme 1, Table 1). A new chiral center is generated at 2-position of the quinoline skeleton during this reaction sequence.[10] Consequently, a 1:1 mixture of diastereomers was obtained for ligands **3a, b**, and **d** containing enantiomerically pure (R_a)-binaphthol. The diastereomeric mixture (R_a,R_C^*)-**3a** was isolated in 56% yield (based on **1**) and the two diastereomers could be separated by column chromatography.[11] The tentative assignment of the configuration at the stereogenic carbon center is based on comparison with ^{1}H and ^{31}P NMR spectroscopic data of related and structurally characterized monodentate 2-alkyl-1,2-dihydroquinoline phosphoramidites.[12]

In a first set of experiments, we used the rhodium-catalyzed hydroformylation of styrene (**4**) to benchmark the potential of QUINAPHOS ligands for asymmetric catalysis (Table 2). The catalysts were prepared in situ from [(acac)Rh(CO)$_2$] (acac = acetylacetonate) and four equivalents of the diastereomeric mixture or the pure diastereomers of **3a**. The reactions were carried out in the neat substrate under otherwise typical hydroformylation conditions. The activities of all three catalysts were well in the range observed with the best chiral hydroformylation catalysts known to date.[13] All catalysts lead to exclusive formation of the hydroformylation products with uniformly high regioselectivity for the desired branched aldehyde **5**.

The enantiomeric excess of **5** showed a dramatic dependence on the absolute configuration at the 2-position of the heterocycle backbone. Use of the diastereomeric mixture (R_a,R_C^*)-**3a** gave a moderate *ee* value of 35.6% in favor of the *S* enantiomer, but almost racemic product was obtained with the R_a,R_C diastereomer. In contrast, the ligand (R_a,S_C)-**3a** gave 74% *ee* for the *S* enantiomer under these nonoptimized reaction conditions. Taking into account regioselectivity *and* enantioselectivity, a remarkable overall selectivity of 84% for the formation of (*S*)-**5** could be achieved with this new ligand.[5, 13–16]

It is interesting to note that the enantiomeric excess observed with the diastereomeric mixture is almost exactly the mean value of the two *ee* values of the single diastereomers. This indicates that the two diastereomers contribute in parallel and with almost identical pathways to the overall reaction,[17] as further supported by the observation that the separated ligands (R_a,R_C)-**3a** and (R_a,S_C)-**3a** resulted in almost identical reaction rates. The rate was significantly lower, however, when the two diastereomers were employed together in form of the mixture (R_a,R_C^*)-**3a**. These results are best rationalized by partial formation of a fairly stable and catalytically nonproductive complex of type [{(R_a,R_C)-**3a**}Rh{(R_a,S_C)-**3a**}]$^+$. The possible implication of this situation for chiral amplification[18] in asymmetric catalysis using QUINAPHOS-type ligands is currently under investigation.

The rhodium-catalyzed hydrogenation of α,β-unsaturated carboxylic acid derivatives also proceeded smoothly in CH$_2$Cl$_2$ at room temperature and elevated pressures, using

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Table 1. ^{31}P NMR spectroscopic data of QUINAPHOS-type ligands **3a–d** (C_6D_6, room temperature).

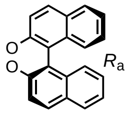
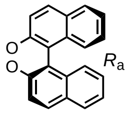
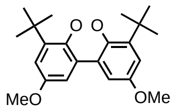
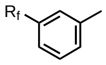
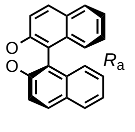
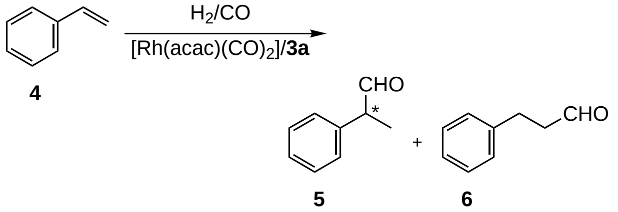
	Config. at C2	Ar	R		$\delta(P_A)$	$\delta(P_B)$	$J(P_AP_B)$ [Hz]
3a	R_C	Ph	*n*Bu		137.5	– 17.8	191.7
	S_C				143.6	– 16.4	131.2
3b	R_C	Ph	*t*Bu		139.0	– 19.2	180.2
	S_C				141.6	– 19.1	85.2
3c	R_C/S_C	Ph	*n*Bu		144.7	– 18.6	202.7
3d	R_C	 $R_f = (CH_2)_2(CF_2)_6F$	*n*Bu		136.9	– 18.3	194.5
	S_C				143.3	– 16.8	130.4

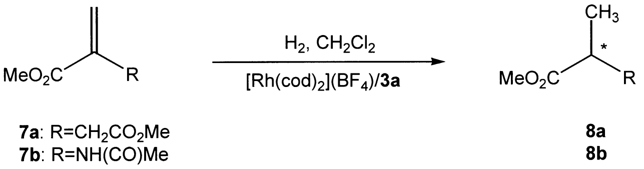
Table 2. Rhodium-catalyzed hydroformylation of styrene (**4**).[a]



Ligand	t [h]	Conversion [%]	TOF[b] [h^{-1}]	**5/6**	*ee* [%]
(R_a,R^*_C)-**3a**	90	54.8	13.4	96.3/3.7	35.6 (*S*)
(R_a,R_C)-**3a**	74	79.3	23.6	96.0/4.0	4.8 (*S*)
(R_a,S_C)-**3a**	70	75.0	23.6	96.7/3.3	74.0 (*S*)

[a] Styrene (**4**, 0.5 mL), **3a** (8×10^{-3} mmol), and $[Rh(acac)(CO)_2]$ (2×10^{-3} mmol) were placed in a stainless-steel high-pressure reactor (V = 11.4 mL) and stirred at $T = 40\,°C$ under $p(CO/H_2,\ 1{:}1) = 100$ bar. [b] Amount of **5** and **6** [mol] per mole of Rh per hour.

Table 3. Enantioselective hydrogenation of dimethyl itaconate (**7a**) and methyl 2-acetamidoacrylate (**7b**).[a]



Substrate	Ligand	**3a**/Rh	Conversion [%]	*ee* [%]
7a	(R_a,S_C)-**3a**	1.1	> 99	64.2 (*R*)
7a	(R_a,S_C)-**3a**	2.2	> 99	78.8 (*R*)
7a	(R_a,R_C)-**3a**	1.1	> 99	95.6 (*R*)
7a	(R_a,R_C)-**3a**	2.2	> 99	98.8 (*R*)
7b	(R_a,R_C)-**3a**	2.2	8.0	12.4 (*S*)
7b	(R_a,R_C)-**3a**	1.0[b]	> 99	97.8 (*S*)

[a] $[Rh(cod)_2](BF_4)$ (2×10^{-3} mmol), **3a**, and **7** (2 mmol) were dissolved in CH_2Cl_2 (2–6 mL) and stirred in a stainless-steel high-pressure reactor (V = 11.4 mL) at room temperature under $p(H_2) = 30$ bar for 24 h. [b] With $[\{(R_a,S_C)$-**3a**$\}Rh(COD)](BF_4)$ **9** as catalyst.

either a catalyst formed in situ from **3a** and $[Rh(cod)_2](BF_4)$ (cod = cyclooctadiene) or the isolated complex $[\{(R_a,R_C)$-**3a**$\}Rh(cod)](BF_4)$ (**9**) as a catalyst precursor (Table 3). In contrast to the observations made for the hydroformylation, the opposite configuration at the chiral carbon atom was required for high *ee* values in the hydrogenation, and (R_a,R_C)-**3a** proved to be the more effective diastereomer. Increasing the amount of ligand during the in situ preparation of the catalyst leads to a marked increase in the enantioselectivity with dimethyl itaconate (**7a**), but was detrimental in the case of the dehydroamino acid ester **7b**.

The rhodium catalysts formed with the QUINAPHOS ligand show not only very high asymmetric induction, but also a significant catalytic activity and stability. Quenching the hydrogenation of **7a** with the preformed complex **9** (**7a**:**9** = 1000:1, $p(H_2) = 50$ bar, room temperature) by venting the reactor after five minutes revealed that product (*R*)-**8a** had already been formed quantitatively with 98.2% *ee*. The reaction mixture remaining in the reactor was charged with a second, larger batch of substrate (**7a**:**9** = 6000:1), pressurized with H_2 ($p = 70$ bar), and vented after 10 min. Hydrogenation was again quantitative and the saturated ester **8a** showed 99.4% *ee* (*R*). The total number of catalytic turnovers in these two consecutive reactions was 7000, and an average turnover frequency (TOF) of 36000 h^{-1} can be estimated as the lower limit for the catalytic activity in the second run. Taking into account the somewhat lower *ee* value obtained in the first run, the second hydrogenation proceeded with almost perfect selectivity for the (*R*) enantiomer (99.6% *ee*).

The previously available large body of data on asymmetric catalysis suggested fairly different design principles for new ligands to be used in rhodium-catalyzed enantioselective hydrogenation and hydroformylation. The majority of highly selective chelating ligands for olefin hydrogenation has a C_2-symmetric structure or at least two closely related binding sites,[2] whereas ligands with highly unsymmetrical structures generally give higher *ee* values in hydroformylation.[13a,15] The *n*Bu-QUINAPHOS phosphane/phosphoramidite ligand **3a** is the first chiral phosphorus ligand for which the formation of highly active and selective rhodium catalysts was observed for hydroformylation as well as for hydrogenation.

2-Alkyl-1,2-dihydroquinoline is a very promising backbone for chiral bidentate phosphorus ligands with two distinct binding sites. The highly flexible synthesis of QUINAPHOS-type ligands opens a broad range of possible modifications for further optimization of the individual members of this ligand family by electronic and steric variation. It is noteworthy in this context that the enantioselectivity obtained with the BINAPHOS-type ligands is largely controlled by their atropisomeric backbones,[5] and structural modifications of this part are difficult. In contrast, the major impact on the asymmetric induction observed with the QUINAPHOS ligand **3a** comes from a "simple" and readily modified stereogenic carbon center that is embedded in a fairly rigid heterocycle skeleton.

Experimental Section

All manipulations were carried out under argon using dried and degassed solvents. The catalysis experiments were carried out in stainless-steel high-pressure reactors according to standard procedures, and the products were analyzed by ^{1}H NMR spectroscopy and GC.

Synthesis of (R_a,R_C^*)-**3a**, (R_a,R_C)-**3a**, and (R_a,S_C)-**3a**. A solution of **1a**[7] (1.0 g, 3.2 mmol) in THF (40 mL) was treated with *n*BuLi in *n*-pentane (1.6 M, 2 mL) at −78 °C and then briefly warmed to 0 °C. The resulting dark red solution was added dropwise to a solution of (*R*)-(1,1′-binaphthalene-2,2′-dioxy)chlorophosphane in THF (20 mL) at −30 °C. After the mixture had slowly warmed to room temperature, the solvent was evaporated and the residue extracted with toluene. Removal of the solvent and crystallization from CH_2Cl_2/ethanol at −20 °C gave colorless (R_a,R_C^*)-**3a** (1.24 g 1.8 mmol, 56%) as a 1:1 mixture of diastereomers.

(R_a,R_C^*)-**3a** (0.24 g) was subjected to column chromatography over dried and degassed silica (Merck, type 9385, 230–400 mesh). Elution with CH_2Cl_2/pentane (1/5) gave a first fraction (0.12 g, 100%) that was assigned as (R_a,R_C)-**3a** on the basis of NMR data.[12] Subsequent elution with pure CH_2Cl_2 gave (R_a,S_C)-**3a** (0.05 g, 42%).

Selected analytical data (see also Table 1):

(R_a,R_C)-**3a**: MS (EI, 70 eV): *m*/*z*: 685 [M^+]; ^{1}H NMR (C_6D_6): $\delta = 7.86$ (d, $J = 8.7$ Hz, 1H, Ar-H), 7.70–7.39 (m, 11H, Ar-H), 7.31 (m, 1H, Ar-H), 7.10–6.84 (m, 11H, Ar-H), 6.78 (m, 1H, Ar-H), 6.39 (d, $^3J = 9.5$ Hz, 1H, CH=CH), 5.72 (dd, $^3J = 9.5$ Hz, $^3J = 5.6$ Hz, 1H, CH=CH), 4.01 (m, 1H, CH), 1.40–0.90 (m, 6H, CH_2), 0.61 (t, $^3J = 7.2$ Hz, 3H, CH_3).

(R_a,S_C)-**3a**: MS (EI, 70 eV): *m*/*z*: 685 [M^+]; ^{1}H NMR (C_6D_6): $\delta = 7.63$–7.57 (m, 6H, Ar-H), 7.51–7.43(m, 2H, Ar-H), 7.28–7.22 (m, 4H, Ar-H), 7.12–6.94 (m, 12H, Ar-H), 6.79 (m, 1H, Ar-H), 6.18 (d, $^3J = 9.6$ Hz, 1H, CH=CH), 5.56 (dd, $^3J = 9.6$ Hz, $^3J = 5.7$ Hz, 1H, CH=CH), 3.88 (m, 1H, CH), 1.40–0.88 (m, 6H, CH_2), 0.73 (t, $^3J = 7.2$ Hz, 3H, CH_3).

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[10] We note that the nitrogen atom is a potential stereogenic center as well.[12]

[11] Alternatively, **2** may be quenched by acid work-up and the resulting enantiomeric amines can be subjected to classical resolution. This approach seems especially attractive for ligands in which the 2-position is the only center of chirality.

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