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Asymmetric Hydrogenation of Quinolines Catalyzed by Iridium Complexes of Monodentate BINOL-Derived Phosphoramidites

Nataša Mršić,[a] Laurent Lefort,[b] Jeroen A. F. Boogers,[b] Adriaan J. Minnaard,[a,*] Ben L. Feringa,[a,*] and Johannes G. de Vries[a,b,*]

[a] University of Groningen , Stratingh Institute, Nijenborgh 4, 9747 AG Groningen, The Netherlands
E-mail: B.L.Feringa@rug.nl
[b] DSM Pharmaceutical Products – Advanced Synthesis & Catalysis, P.O. Box 18, 6160 MD Geleen, The Netherlands
Fax: (+31)-46-476-7604; e-mail: Hans-JG.Vries-de@dsm.com

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Dedicated to Prof. Dr. Andreas Pfaltz on the occasion of his 60th birthday.

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Abstract: The monodentate BINOL-derived phosphoramidite PipPhos is used as ligand for the iridium-catalyzed asymmetric hydrogenation of 2- and 2,6-substituted quinolines. If tri-*ortho*-tolylphosphine and/or chloride salts are used as additives enantioselectivities are strongly enhanced up to 89%. NMR indicates that no mixed complexes are formed upon addition of tri-*ortho*-tolylphosphine.

Keywords: asymmetric hydrogenation; homogeneous catalysis; iridium; phosphoramidites; quinolines

Introduction

Aymmetric hydrogenation of unsaturated prochiral compounds represents an attractive and versatile method for the preparation of enantiopure building blocks.[1,2] Although significant effort has been made in the area of asymmetric hydrogenation of aromatic and heteroaromatic compounds,[3] many challenges remain. Enantiopure tetrahydroquinolines represent important synthetic intermediates, as they are present in numerous alkaloids and biologically active compounds.[4] Transition metal-catalyzed asymmetric hydrogenation of quinolines is one of the best methods for their preparation, as many substituted quinolines are commercially available.

In recent years, a number of examples of asymmetric hydrogenation of quinolines with high enantioselectivities were published.[5–9] In 2003 Zhou et al. reported the use of Ir complexes generated *in situ* from $[Ir(COD)Cl]_2$ and (*R*)-MeO-Biphep[6] or ferrocenyloxazoline-derived P,N ligands[8] (up to 96% *ee*). Similar results were described subsequently by Chan et al. using only 0.1 mol% of a catalyst based on a diphosphinite ligand.[9] In 2006 Reetz reported the use of a combination of bis-phosphonites and monodentate achiral phosphorus ligands (up to 96% *ee*).[7]

In 2007, Zhou et al. reported the use of (*S*)-Segphos as chiral ligand in the iridium-catalyzed transfer hydrogenation of quinolines with Hantzsch esters (up to 91% *ee*).[10] The *ee* is strongly determined by the ester groups of the Hantzsch ester.

An asymmetric organocatalytic transfer hydrogenation of heteroaromatic compound was reported by Rueping in 2006.[11] The catalysts are bulky BINOL-derived phosphoric acids and Hantzsch esters were used as stoichiometric hydrogen source (up to >99% *ee*).

Bidentate chiral ligands were considered superior over monodentate ones in metal-catalyzed asymmetric hydrogenation for more than 30 years[1] as chelation was believed to be necessary to impart the rigidity to the metal complex for an efficient transfer of chirality. Recently chiral monodentate phosphines, phosphonites, phosphoramidites and phosphites were reported to lead to excellent results in the asymmetric hydrogenation of α- and β-dehydroamino acids, itaconic acid derivatives, and enamides.[12] Monodentate phosphoramidite ligands have the advantage of being readily accessible, highly diverse, air stable and inexpensive compared to most bidentate ligands.[13] In addition, they are amenable to parallel synthesis.[14]

We have developed the use of monodentate phosphoramidites as ligands for asymmetric hydrogena-

tion,[15–17] conjugate addition[18], allylic alkylation,[19] asymmetric arylation of aldehydes,[20] ketones[21,22] and substituted imines.[23] Herein we report the first asymmetric hydrogenation of quinolines catalyzed by iridium complexes based on monodentate BINOL-derived phosphoramidites.

Results and Discussion

Asymmetric hydrogenation of quinaldine (**1a**) was chosen as a model reaction (Scheme 1). Initial hydrogenation experiments were performed at 25 bar of hydrogen pressure and 60 °C, using 1 mol% of catalyst with L*/Ir = 2/1, prepared *in situ*. Using (*S*)-1-(3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a'*]dinaphthalen-4-yl)-piperidine (PipPhos) as ligand L* and [Ir(COD)Cl]$_2$ as iridium source, we were able to obtain up to 36% *ee* and 96% conversion over 24 h. Initial solvent screening showed that the enantioselectivity of the reaction is solvent-dependent. The best result was obtained in the non-polar solvent toluene (Table 1, entry 7), whereas use of protic solvents such as MeOH and *i*-PrOH resulted in low enantioselectivity and somewhat lower conversions (entries 1 and 2).

These results encouraged us to screen more phosphoramidite ligands in toluene. High throughput experimentation (HTE)[14,24] is a methodology where a large number of ligands are quickly synthesized and tested in parallel. It has the added advantage that in addition to the chiral ligands, substrates, additives, solvents and reaction conditions can also be screened. Although 48 different phosphoramidites and phosphites based on BINOL, 8H-BINOL, and 3,3′-dimethyl-BINOL were tested, as well as two iridum precursors ([Ir(COD]Cl]$_2$ and Ir(COD)$_2$BF$_4$) we were not able to reach higher enantioselectivities. Additional monodentate and bidentate BINOL, TADDOL, biphenol and catechol-based phosphoramidites and phosphites were also tested, to no avail.

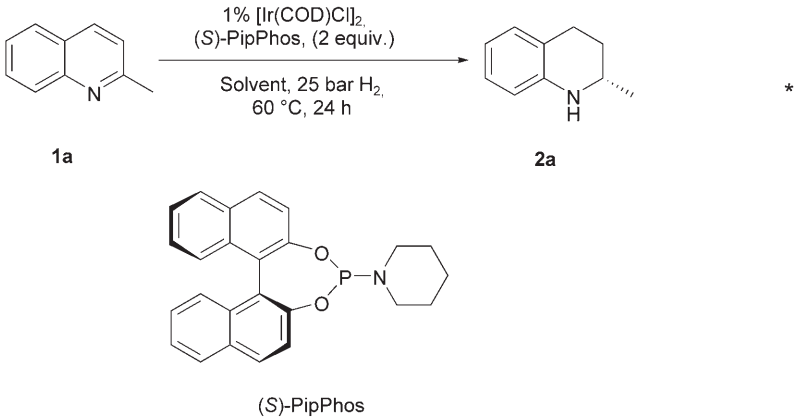
Table 1. Solvent variation in the asymmetric hydrogenation of quinaldine (**1a**).[a]

Entry	Solvent	Conversion[b] [%]	*ee*[c] [%]
1	*i*-PrOH	91	9
2	MeOH	47	11
3	THF	97	21
4	Acetone	97	18
5	EtOAc	96	28
6	CH_2Cl_2	96	18
7	Toluene	96	**36**

[a] *Reaction conditions:* 1-mmol scale, quinoline/[Ir(COD)Cl$_2$]$_2$/(*S*)-PipPhos = 100/1/4, 4 mL of solvent, 60 °C 25 bar H_2, 24 h.
[b] Conversions were determined by GC.
[c] Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

Surprisingly, it was observed that upon addition of 10 mol% of piperidine hydrochloride to the standard hydrogenation reaction based on PipPhos and [Ir(COD]Cl]$_2$ in toluene the enantioselectivity increased to 63%. This positive effect was observed over a broad range of chloride/metal ratios, from 2–100%. We will discuss this finding in more detail further in this paper. In most hydrogenations described hereafter we have used this additive.

Both Reetz[25–27] and ourselves[28] have shown that the use of mixtures of chiral monodentate ligands can improve enantioselectivity and reactivity. A mixed ligand approach has been employed in rhodium[17,25,28,29] and iridium-catalyzed[7] asymmetric hydrogenations and in rhodium-catalyzed additions of boronic acids.[22] It is also possible to use mixed complexes based on a monodentate chiral ligand and a non-chiral phosphorus ligand.[17,26] The fact that the structure of monodentate ligands can be varied easily enables us to screen a very large number of different complexes in the asymmetric hydrogenation. Since the catalytically active species most likely contains



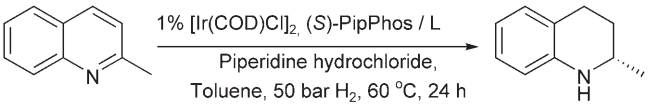
Scheme 1. Asymmetric hydrogenation of quinaldine (**1a**).

two monodentate ligands, two homo-complexes, $Ir(L^1)_2$ and $Ir(L^2)_2$, and the hetero-complex $Ir(L^1L^2)$ will be formed simultaneously. The hetero-complex represents a new catalyst, and if it is endowed with higher activity and selectivity than the two homo-complexes, it will lead to better results.

We thus screened mixtures of (*S*)-PipPhos and achiral phosphine ligands in the asymmetric hydrogenation of quinaldine (**1a**). Reactions were performed under 50 bar of H_2 pressure in order to obtain full conversions over 24 h. The results are shown in Table 2. It was noticed that *ortho*-substituted phosphines, as well as tri-*tert*-butylphosphine lead to good conversions and high enantioselectivities (Figure 1). Surprisingly, the catalyst prepared from PipPhos and triphenylphosphine leads to very low conversion (entry 1). The best result was obtained using PipPhos and **L1**, giving full conversion and 83% *ee* (entry 2). High conversions were also obtained when **L2** and **L6** were used in combination with PipPhos (entries 3 and 7).

Since the $[Ir(COD]Cl]_2$/tri-*o*-tolylphosphine/PipPhos/piperidine hydrochloride catalytic system gave the best result in the asymmetric hydrogenation of quinaldine (**1a**) we further studied the effect of addition of different salts with this system (Table 3). We observed that all tested chloride salts induced high enantioselectivities. Cesium fluoride blocked the catalyst activity completely (entry 5), whereas potassium bromide and tetrafluoroborate (entries 6 and 8) led to high conversions although the enantioselectivities were somewhat lower. Addition of potassium iodide also had a negative effect on the enantioselectivity

Table 2. Asymmetric hydrogenation of quinaldine (**1a)** using a mixture of monodentate ligands[a]



1a 2a

Entry	Phosphine	Conversion[b] [%]	*ee*[c] [%]
1	PPh_3	2	nd
2	**L1**	100	83
3	**L2**	100	70
4	**L3**	41	81
5	**L4**	54	82
6	**L5**	18	77
7	**L6**	98	78

[a] *Reaction conditions:* 1-mmol scale, quinoline/[Ir(COD)Cl_2]$_2$/(*S*)-PipPhos/phosphine/piperidine hydrochloride = 100/1/4/2/10, 4 mL of toluene, 60 °C 50 bar H_2, 24 h.
[b] Conversions were determined by GC.
[c] Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

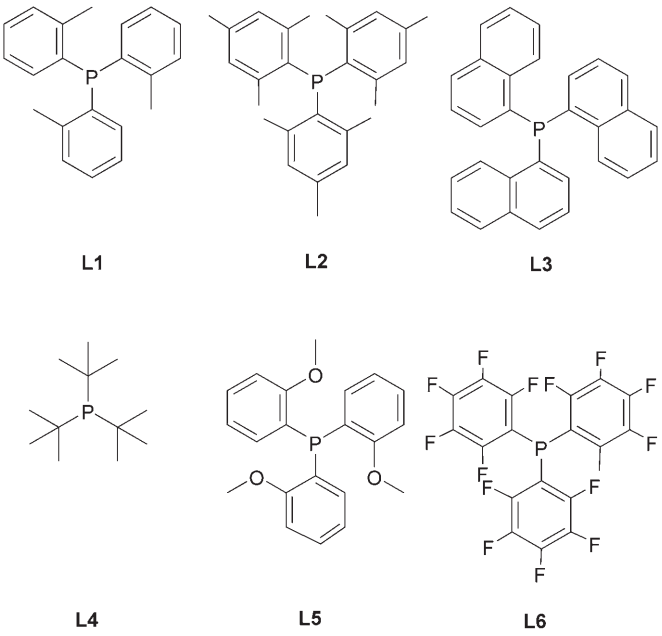
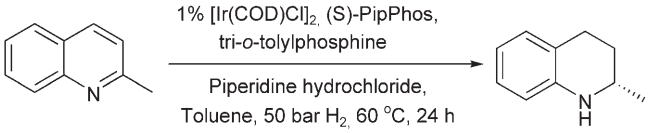


Figure 1. Achiral phosphines used in the mixed monodentate ligand approach.

Table 3. Effect of the addition of salts on the enantioselectivity of the asymmetric hydrogenation of quinaldine (**1a**).[a]



1a 2a

Entry	Salt	Conversion[b] [%]	*ee*[c] [%]
1	-	100	63
2	Piperidine·HCl	100	83
3	KCl	100	83
4	Et_3N·HCl	98	81
5	CsF	0	-
6	KBr	100	69
7	KI	98	30
8	KBF_4	98	77

[a] *Reaction conditions:* 1-mmol scale, quinoline/[Ir(COD)Cl_2]$_2$/(*S*)-PipPhos/tri-*o*-tolylphosphine/salt = 100/1/4/2/10, 4 mL toluene, 60 °C, 50 bar H_2, 24 h.
[b] Conversions were determined by GC.
[c] Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

(entry 7). Since with potassium chloride irreproducible results were obtained, piperidine hydrochloride was chosen as the additive for further screenings.

To obtain more information on the relative effect of the additional ligand and the salt we screened all possible additive combinations in toluene and in dichloromethane in the asymmetric hydrogenation of **1a** (Table 4). The use of 10 mol% of piperidine hydro-

Table 4. Effect of the addition of piperidine hydrochloride on the *ee* in the asymmetric hydrogenation of **1a**.[a]

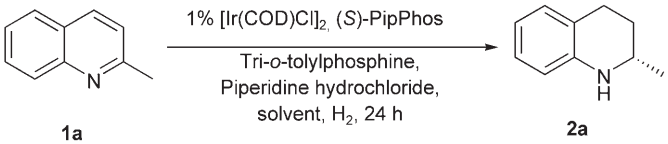
Entry	Solvent	L*	L	Additive	Conversion[b] [%]	*ee*[c] [%]
1	DCM	PipPhos	-	-	100	18
2	DCM	PipPhos	-	Piperidine·HCl	100	83
3	DCM	PipPhos	P(*o*-tol)$_3$		100	69
4	DCM	PipPhos	P(*o*-tol)$_3$	Piperidine·HCl	100	89
5	Toluene	PipPhos	-	-	100	36
6	Toluene	PipPhos	-	Piperidine·HCl	100	63
7	Toluene	PipPhos	P(*o*-tol)$_3$	-	100	67
8	Toluene	PipPhos	P(*o*-tol)$_3$	Piperidine·HCl	100	83

[a] *Reaction conditions:* 1-mmol scale, quinoline/[Ir(COD)Cl$_2$]$_2$/(*S*)-PipPhos/tri-*o*-tolylphosphine/piperidine hydrochloride = 100/1/4/2/10, 4 mL solvent, 60 °C, 50 bar H_2, 24 h.
[b] Conversions were determined by GC.
[c] Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

chloride as the sole additive in dichloromethane led to an increase in enantioselectivity from 18 to 83% (entries 1 and 2). In the mixed ligand system, the addition of chloride improved the enantioselectivity from 69 to 89% (entries 3 and 4). A similar effect is observed in toluene where using piperidine hydrochloride as the sole additive led to an increase in the enantioselectivity from 36 to 63% (entries 5 and 6), whereas adding the hydrochloride salt to the mixed ligand system led to an increase in *ee* from 67 to 83% (entries 7 and 8). It was even possible to hydrogenate the hydrochloride salt of **1a** in toluene without loss in enantioselectivity although a longer reaction time (48 h) was necessary, perhaps due to the lower solubility of the substrate.

The effects of solvent, pressure and temperature on the conversion and enantioselectivity were also investigated using the [Ir(COD)Cl]$_2$/PipPhos/phosphine/piperidine hydrochloride catalytic system. The results are summarized in Table 5. It was observed that the rate of the reaction strongly depends on the temperature. Conversions greater than 97% were achieved in all aprotic solvents at 60 °C or higher. At lower temperatures the reaction is much slower (entries 3, 6 and 13). The rate of the reaction depends on the hydrogen pressure, but importantly, the enantioselectivity stays the same for pressures above 10 bar, in keeping with earlier findings in olefin hydrogenation.[16] The best result (quantitative conversion and 89% *ee*) was achieved in dichloromethane at 50 bar of pressure and 60 °C.

Table 5. Asymmetric hydrogenation of quinaldine (**1a**).[a]



1a 2a

Entry	Solvent	H_2 [bar]	*T* [°C]	Conv.[b] [%]	*ee*[c] [%]
1	Toluene	100	80	97	77
2	Toluene	100	60	100	83
3	Toluene	100	40	24	77
4	Toluene	70	80	97	78
5	Toluene	70	60	98	82
6	Toluene	70	40	11	79
7	Toluene	50	60	100	83
8	Toluene	25	60	100	83
9	CH_2Cl_2	50	60	100	**89**
10	CH_2Cl_2	25	60	100	87
12	CH_2Cl_2	10	60	40	87
13	CH_2Cl_2	50	40	7	nd
14	MeOAc	50	60	100	88
15	EtOAc	50	60	100	87
16	*i*-PrOAc	50	60	100	87
17	$ClCH_2CH_2Cl$	50	60	100	87
18	Acetone	50	60	100	80
19	*i*-PrOH	50	60	91	65

[a] Reaction conditions: 1-mmol scale, quinoline/[Ir(COD)Cl$_2$]$_2$/(*S*)-PipPhos/tri-*o*-tolylphosphine/piperidine hydrochloride = 100/1/4/2/10, 4 mL solvent, 24 h.
[b] Conversions were determined by GC.
[c] Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

Kinetics

In order to examine the stability of the catalyst during the reaction, the enantioselectivity was monitored over time (Figure 2a). An increase of the enantioselectivity over 24 h was observed. The low *ee* at the beginning of the reaction may be explained by the slow formation of the catalytically active species during the first hour (10% of conversion). This is also confirmed by the induction time that is observed in the hydrogenation (Figure 2b). We tried to overcome this drawback by pre-stirring the iridium complex in the presence of the ligand under the reaction conditions during 1 h, followed by the addition of the sub-

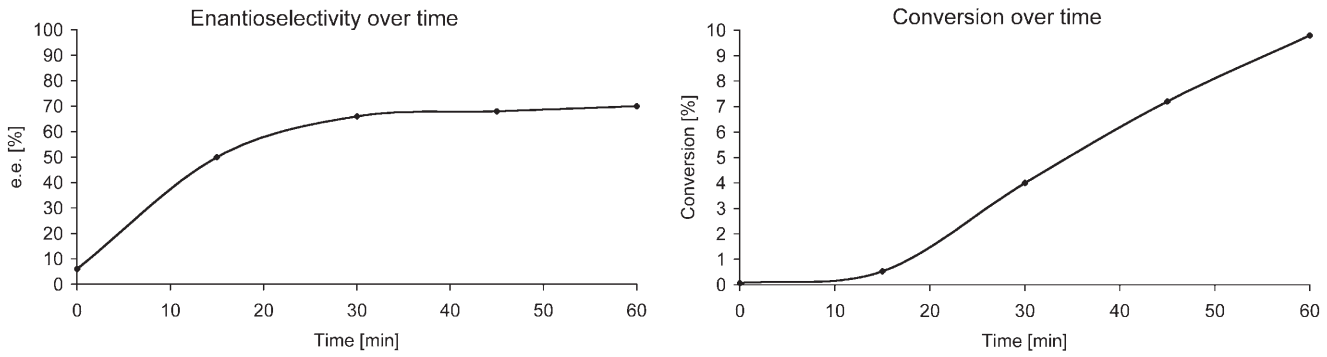


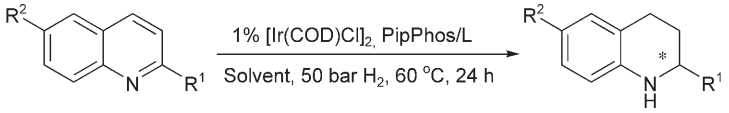
Figure 2. Kinetics of the asymmetric hydrogenation of quinaldine (**1a**). *Reaction conditions:* 1-mmol scale, quinoline/[Ir(COD)Cl$_2$]$_2$/(*S*)-PipPhos/tri-*o*-tolylphosphine/piperidine hydrochloride = 100/1/4/2/10, 4 mL solvent, 24 h. Conversion was determined by GC and enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column.

strate. Unfortunately, this did not improve the enantioselectivity of the reaction.

Under the optimized conditions, a variety of substituted quinolines was hydrogenated using the [Ir(COD]Cl]$_2$/PipPhos/phosphine/piperidine hydrochloride catalytic system in toluene or dichloromethane. The best results are summarized in Table 6.

All quinolines studied were hydrogenated with high conversions and enantioselectivities. The best results were obtained with methyl- and *i*-Pr-substituted quinoline (89% *ee*, entries 1 and 3), while the lowest enantioselectivity was obtained with benzyl-substituted quinoline (76% *ee*, entry 7). Introduction of electron-donating or withdrawing substituents in 6-position did not affect the enantioselectivity significantly (entries 5–7), whilst introduction of longer alkyl chains resulted in a small drop of *ee*. (entries 8 and 9).

Table 6. Asymmetric hydrogenation of 2,6-substituted quinolines using (*S*)-PipPhos and achiral ligands **L1–L6**.[a]

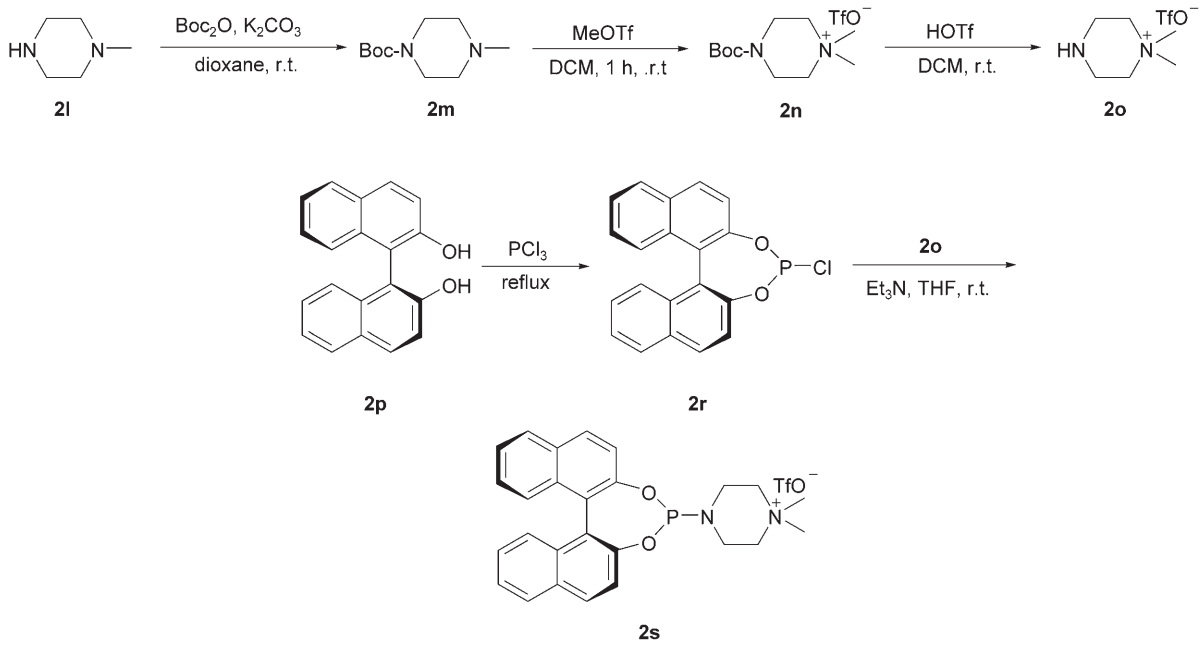


2

1a R^1 = Me, R^2 = H
1b R^1 = Et, R^2 = H
1c R^1 = *i*-Pr, R^2 = H
1d R^1 = *i*-Bu, R^2 = H
1e R^1 = Me, R^2 = Me
1f R^1 = Me, R^2 = MeO
1g R^1 = Me, R^2 = F
1h R^1 = *n*-Pentyl, R^2 = H
1i R^1 = *n*-Hexyl, R^2 = H
1j R^1 = Benzyl, R^2 = H
1k R^1 = Ph, R^2 = H

	Solvent	R^1/R^2	Ligand	Conversion[b] [%]	*ee*[c] [%]	Configuration[d]
1	DCM	Me/H (**2a**)	**L1**	100	89	(*S*)
2	DCM	Et/H (**2b**)	**L1**	100	88	(*S*)
3	Toluene	*i*-Pr/H (**2c**)	**L1**	100	89	(*R*)
4	Toluene	*i*-Bu/H (**2d**)	**L1**	98	86	nd
5	DCM	Me/Me (**2e**)	**L1**	100	85	(*S*)
6	DCM	Me/MeO (**2f**)	**L1**	73	82	(*S*)
7	DCM	Me/F (**2g**)	**L5**	100	88	(*S*)
8	DCM	*n*-Pentyl/H (**2h**)	**L1**	100	83	(*S*)
9	DCM	*n*-Hexyl/H (**2i**)	**L1**	100	78	nd
10	DCM	Benzyl/H (**2j**)	**L1**	100	76	nd
11	Toluene	Ph/H (**2k**)	**L6**	88	88	(*S*)

[a] *Reaction conditions:* 1-mmol scale, quinoline/[Ir(COD)Cl$_2$]$_2$/(*S*)-PipPhos/phosphine/piperidine hydrochloride = 100/1/4/2/10, 4 mL solvent, 60 °C, 50 bar H_2, 24 h.
[b] Conversions were determined by ^{1}H NMR.
[c] Enantiomeric excess was determined by GC and HPLC.
[d] Absolute configuration of the product is assigned by comparison with literature data.



Scheme 2. Preparation of quaternized ligand **2s**.

Mechanistic Discussion

In order to gain understanding of the mechanism of the reaction, high pressure ^{31}P NMR experiments were performed on the asymmetric hydrogenation of **1a** using a mixture of PipPhos and achiral phosphine (2:1) as ligands at 60 °C and 25 bar of H_2 pressure. To our surprise, no mixed ligand iridium species were observed when tri-*o*-tolylphosphine was used as achiral phosphine. A large tri-*ortho*-tolylphosphine peak was visible in the NMR prior to and throughout the hydrogenation reaction. In the case of triphenylphosphine and PipPhos, mixed ligand species were observed, however, this catalyst gave only 2% conversion in the hydrogenation of **1a**. It should be added that addition of other unhindered ligands such as triphenyl phosphite (not shown in Table 2) also led to almost no conversion. These results suggests that *o*-substituted achiral phosphines are perhaps sterically too demanding for coordination to the iridium together with PipPhos, making it impossible to form a mixed ligand species. In addition, no difference was observed between the ^{31}P NMR spectra of the reactions with and without added piperidine hydrochloride. Despite the significant improvement of the selectivity, the role of the achiral phosphine and chloride salt has not been elucidated until now. However, it is known that iridium catalysts tend to decompose to inactive hydride-bridged clusters in the absence of substrate.[12,30] If the substrate is a weak ligand, this decomposition can be competitive with hydrogenation. It is conceivable that the chloride salt prevents the formation of poorly active iridium clusters. The role of the added phosphine ligand is even more obscure. It may just serve as a scavenger of traces of oxygen. It is also possible that mixed ligand species are formed in one or more intermediates of the catalytic cycle but not in the resting state, thus making them unobservable.

Mass spectral studies into the nature of the catalyst were hampered by the fact that these catalysts are neutral species and thus lead to feeble signals in ES-MS. To solve this problem we decided to develop an analogous catalyst which carries a positive charge in the ligand. This approach has been used with great success by Chen in his MS study of metathesis catalysts.[31]

Thus, we prepared quaternized ligand **2s** (Scheme 2). The synthesis starts with Boc-protection of 1-methylpiperazine (**2m**), followed by methylation with methyl triflate in dichloromethane at room temperature, and deprotection with triflic acid. The prepared quaternized amine **2o** was isolated in 76% yield. (*S*)-BINOL was refluxed in neat PCl_3 in order to obtain chlorophosphite **2r**. This was stirred with **2n** in the presence of triethylamine in THF to give the quaternized phosphoramidite **2s** in overall 27% yield.

Unfortunately, the results in the iridium-catalyzed hydrogenation of **1a** with ligand **2s** were dramatically different from the results obtained with PipPhos (Table 7). Thus, this ligand cannot be assumed to be a good model compound for PipPhos. In spite of this we did an ES-MS analysis of the hydrogenation reactions of Table 7. In all MS very minor peaks of iridium complexes were observable, none of which could be associated with **2s**. In addition, the spectra showed

Table 7. Asymmetric hydrogenation of quinaldine (**1a**) using quaternized ligand **2s**.[a]

Entry	**2s**/PipPhos/P(*o*-tol)$_3$/Cl$^-$/Ir	Conversion[b] [%]	*ee*[c] [%]
1	1/1/0/0/1	31	3
2	1/1/1/0/1	0	-
3	1/1/1/5/1	4	44
4	1/1/0/5/1	19	12
5	2/0/0/0/1	41	6
6	2/0/1/0/1	6	7
7	2/0/1/5/1	2	18

[a] *Reaction conditions:* 1-mmol scale, 4 mL of dichloromethane, 60 °C, 25 bar H_2, 2 h.
[b] Conversions were determined by GC.
[c] Enantiomeric excess was determined by GC analysis with Chiralsil DEX CB column

only very small peaks of the molecular ion of **2s**. We have not yet arrived at a satisfactory explanation for these results. One possibility is that the majority of the iridium is present in the form of nanoparticles, stabilized by **2s**.

Although low enantioselectivities were obtained in the asymmetric hydrogenation of quinaldine (**1a**) using quaternized ligand **2s**, it was observed that using 2 equivalents of **2s** per iridium atom, hydrogenation is much faster than with PipPhos, giving 41% conversion within 2 h (entry 5). Moreover, using mixture of **2s** and PipPhos (1:1) reaction is still significantly faster (entry 1).

Conclusions

The combination [Ir(COD)Cl]$_2$/PipPhos/tri-*ortho*-tolylphosphine/piperidine·HCl is a good catalyst for the enantioselective hydrogenation of 2- and 2,6-substituted quinolines. Full conversions and enantioselectivities up to 89% were obtained.

Experimental Section

General Experimental Procedure for Hydrogenation

A mixture of [Ir(COD)Cl]$_2$ (6.72 mg, 0.01 mmol), (*S*)-1-(3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl)-piperidine [(*S*)-PipPhos] (15.98 mg, 0.04 mmol), achiral phosphine (0.02 mmol), substrate (1 mmol) and piperidine hydrochloride (12.16 mg, 0.1 mmol) were dissolved in 4 mL of solvent, in a glass vial. The vial was placed in a stainless steel autoclave. Hydrogenation was performed at 60 °C under 50 bar of hydrogen pressure for 24 h. After cooling the autoclave, hydrogen pressure was carefully released. The reaction mixture was flushed over a short silica column. Solvent was removed under vacuum and conversion was determined by GC or NMR. Crude product was purified by chromatography (silica gel, heptane/EtOAc = 4/1).

2,2-Dimethylpropionic Acid 4-methyl-piperazin-1-yl Ester (2m)

To a solution of 1-methylpiperazine (5 g, 50 mmol) in dioxane (100 mL) di-*tert*-butyl dicarbonate (11.98 g, 55 mmol) and potassium carbonate (7.59 g, 55 mmol) were added and reaction mixture was stirred over night at room temperature. The resulting mixture was washed with water (100 mL) and water layer was extracted with ethyl acetate (100 mL). The combined organic layers were dried on anhydrous magnesium sulfate and filtered. The solvent was removed under vacuum, and **2m** was isolated as a yellow oil; yield: 9.1 g (92%).

1,1-Dimethylpiperazinium Trifluoromethanesulfonate (2o)

To a solution of 4-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (7.1 g, 35.4 mmol) in dry dichloromethane (50 mL), methyl triflate was added dropwise (4 mL, 35.4 mmol). The reaction was stirred at room temperature over 1 h, followed by addition of triflic acid (4.97 mL, 56.2 mmol). After 1 h, the solvent was decanted and 50 mL of methanol were added. After stirring for 15 min the precipitated white solid was filtered off and dried to afford the quaternized amine **2o**; yield: 7.63 g (82%).

(*S*)-4-(3,5-Dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinaphthalen-4-yl)-1,1-dimethylpiperazinium Trifluoromethanesulfonate (2s)

In a Schlenk tube (*S*)-BINOL (1.5 g, 5.24 mmol) was refluxed in neat phosphorus trichloride (5 mL) over night. After cooling the reaction mixture, the excess of phosphorus trichloride was distilled off and the resulting phosphorus chloride (**2r**) was washed with dry toluene (3×5 mL), and dissolved in dry THF (5 mL). In another Schlenk tube quaternized amine **2o** (1.38 g, 5.24 mmol) and triethylamine (726 μL, 5.24 mmol) were dissolved in 5 mL of THF. The solution of **2r** was then added to the solution of **2o** and triethylamine at 0 °C. After 10 min, the reaction mixture was warmed to room temperature and stirred overnight. The precipitated crystals were filtered off and ether was added (10 mL). The newly formed white precipitate was filtered off and washed with dichloromethane to afford pure phosphoramidite **2s**; yield: 1.09 g (36%).

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