Threonine-Derived Phosphinite-Oxazoline Ligands for the Ir-Catalyzed Enantioselective Hydrogenation

Frederik Menges, Andreas Pfaltz*

Department of Chemistry, University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland
Fax: (+41)-61-267-1103, e-mail: andreas.pfaltz@unibas.ch

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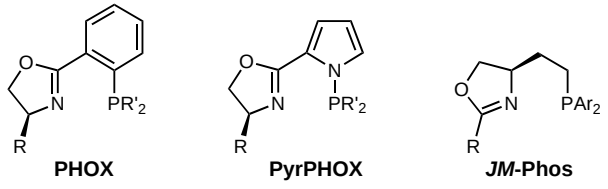
Abstract: A series of chiral phosphinite-oxazolines was synthesized in four steps starting from carboxylic acids and threonine methyl ester. In the asymmetric hydrogenation of a number of alkenes, iridium complexes of these ligands induced significantly higher enantioselectivities than the corresponding serine-derived complexes. Enantiomeric excesses of 89 to 99% were obtained for unfunctionalized alkenes with turnover numbers of up to 5000.

Keywords: asymmetric catalysis; hydrogenation; iridium; ligand design; N,P-ligands.

Iridium complexes derived from chiral phosphinooxazolines (PHOX ligands)[1] are efficient catalysts for the enantioselective hydrogenation of imines[2] and olefins.[3] Particularly promising results were obtained in the hydrogenation of unfunctionalized olefins, a class of substrates that cannot be handled by conventional rhodium- and ruthenium-phosphine catalysts.[4] Although iridium-PHOX catalysts gave excellent enantioselectivities and high turnover numbers in the hydrogenation of certain olefins such as 1,2-diaryl-1-alkyl-substituted alkenes, the substrate scope of these catalysts proved to be limited. Therefore, we and others started a search for new P,N-ligands which enhance the application range of iridium-catalyzed hydrogenation.

Burgess and coworkers reported the *JM*-Phos ligands[5] (Figure 1) and, more recently, analogous oxazolines connected to an imidazolylidene instead of a phosphine group.[6] We prepared PHOX analogues (PyrPHOX; Figure 1) in which the phenyl bridge was replaced by a pyrrole ring. These ligands gave high enantioselectivities in the hydrogenation of the α,β-unsaturated ester **9** (92% ee, structure see Table 1) and the dihydronaphthalene derivative **10** (92% ee).[7] The most promising class of ligands that we have found so far are the phosphinite-oxazolines **1**.[8,9] They gave good to excellent



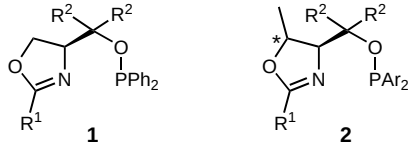
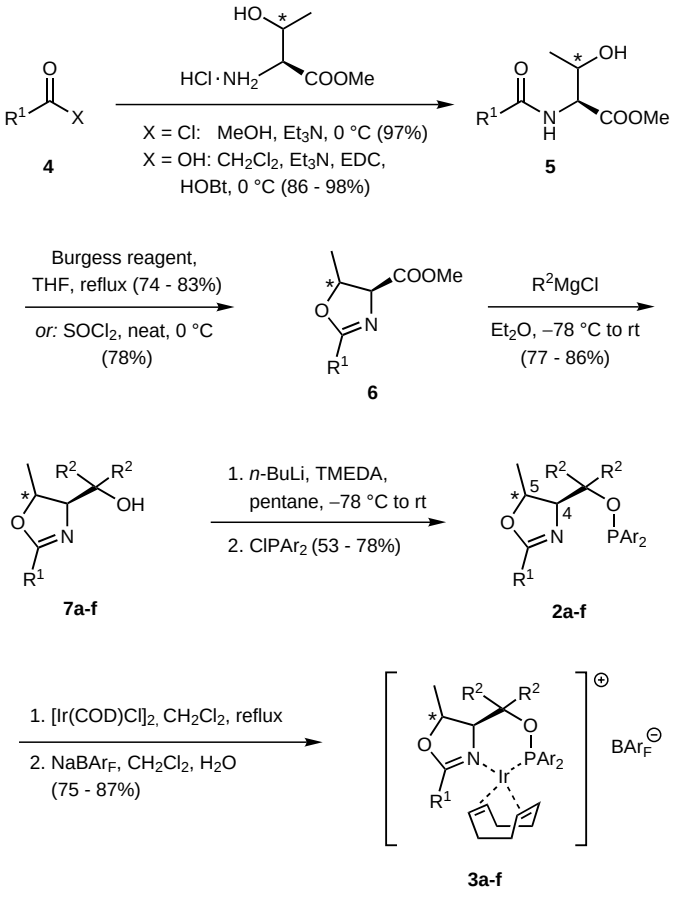


Figure 1. P,N-Ligands for enantioselective iridium-catalyzed hydrogenation.



a: R^1 = Ph;	R^2 = Bn;	Ar = Ph;	4*S*,5*S*
b: R^1 = Ph;	R^2 = Bn;	Ar = Ph;	4*S*,5*R*
c: R^1 = Ph;	R^2 = Bn;	Ar = *o*-Tolyl;	4*S*,5*S*
d: R^1 = Ph;	R^2 = Me;	Ar = Ph;	4*S*,5*S*
e: R^1 = 3,5-$Me_2C_6H_3$;	R^2 = Bn;	Ar = Ph;	4*S*,5*S*
f: R^1 = 3,5-*t*-$Bu_2C_6H_3$;	R^2 = Bn;	Ar = Ph;	4*S*,5*S*

Scheme 1. Synthesis of threonine derived phosphinite-oxazoline ligands. EDC: *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, HOBt: 1-hydroxybenzotriazole, BAr_F: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

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enantioselectivities for a much wider range of substrates than the other P,N-ligands studied so far. Another advantage of this ligand system is its modular architecture allowing the introduction of many different substituents at the oxazoline ring, the backbone and the phosphine group. The synthesis is straightforward, starting from serine methyl ester as an inexpensive precursor which is available in both enantiomeric forms.

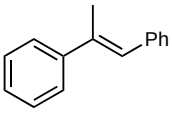
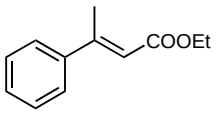
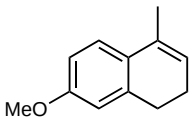
As an extension of this work, we report here the synthesis of analogous phosphinite-oxazolines **2** derived from threonine and their application in the Ir-catalyzed hydrogenation. Surprisingly, the additional methyl group in the oxazoline ring was found to have a remarkably strong effect on the enantioselectivity resulting in distinctly higher enantiomeric excesses for a number of substrates.

The synthesis starts with threonine methyl ester hydrochloride which is coupled with the carboxylic acid **4** using either EDC/HOBt or thionyl chloride for activation (Scheme 1). Formation of the oxazolines **6** can be achieved with Burgess reagent[10] or with neat $SOCl_2$.[11,12] This ring closure follows an S_N2-like pathway, so the stereogenic center at C(5) is inverted.[11] Therefore, starting from L-(2*S*,3*R*)-threonine, the (4*S*,5*S*)-product **6** is formed.[13] Addition of a Grignard reagent to the ester **6** results in the corresponding hydroxyoxazoline **7** in good yield. After deprotonation of the tertiary alcohol with *n*-butyllithium/TMEDA and condensation with a chlorophosphine, the phosphinite-oxazolines **2** are obtained in moderate to good yields. The corresponding iridium-complexes **3** are synthesized according to standard procedures.[3] The resulting complexes are air- and moisture-stable and can be purified by column chromatography on silica gel.

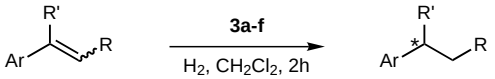
To study the influence of the relative configuration at the two stereogenic centers, both diastereomers (**2a** and **2b**) of one ligand were synthesized. For examining the role of the R^1 substituent, the steric demand in this position was increased stepwise by replacing the phenyl (**2a**) by a 3,5-dimethylphenyl (**2e**) and a 3,5-di(*tert*-butyl)phenyl (**2f**) group. The substituent at the phosphorus atom was also varied by introduction of *ortho*-tolyl substituents (**2c**). To investigate if bulky R^2 groups are required for good selectivities, the dimethyl derivative **2d** was synthesized. In initial experiments the iridium complexes **3a** and **3b** were tested in the enantioselective hydrogenation of a series of olefins (Scheme 2) and the results were compared with the enantioselectivities previously obtained with the corresponding serine-derived catalyst.[8]

In the hydrogenation of substrates **8**, **9** and **10**, the threonine-derived catalysts **3a** and **3b** proved to be superior to the corresponding serine-derived complex [Ir(COD) (**1**)] (R^1 = Ph, R^2 = Bn, Table 1). In the hydrogenation of *trans*-α-

Table 1. Enantioselective hydrogenation of olefins with catalysts **3a** – **3f**.[a]

Entry	Substrate	Catalyst	Cat. loading [mol %]	Conv.[b] [%]	ee[c] [%]
1	 **8**	**3a**	1	100	99 (*R*)
2		[Ir(COD) (**1**)][d]	0.3	100	89 (*S*)
3		**3b**	1	100	97 (*R*)
4		**3c**	1	100	98 (*R*)
5		**3d**	1	100	98 (*R*)
6		**3e**	1	100	99 (*R*)
7		**3f**	1	100	99 (*R*)
8		**3a**	0.5[e]	100	99 (*R*)
9		**3a**	0.1[e]	100	99 (*R*)
10		**3a**	0.05 [e]	> 99	99 (*R*)
11		**3a**	0.02[e, f]	100	99 (*R*)
12		**3a**	0.01[g]	54	99 (*R*)
13	 **9**	**3a**	1	> 99	92 (*R*)
14		[Ir(COD) (**1**)][d]	0.1	61	85 (*S*)
15		**3b**	1	97	85 (*R*)
16		**3c**	1	> 99	70 (*R*)
17		**3d**	1	> 99	88 (*R*)
18		**3e**	**1**	> **99**	**94 (*R*)**
19		**3f**	1	96	61 (*R*)
20	 **10**	**3a**	1	100	71 (*S*)
21		[Ir(COD) (**1**)][d]	0.6	100	55 (*R*)
22		**3b**	**1**	**100**	**85 (*S*)**
23		**3c**	1	100	66 (*S*)
24		**3d**	1	100	65 (*S*)
25		**3e**	1	100	74 (*S*)
26		**3f**	1	100	64 (*S*)

[a] All reactions were performed using 0.1 mmol of alkene and 1 mL of dichloromethane at 50 bar of hydrogen pressure at rt (reaction time: 2 h).
[b] Conversion was determined by GC. In all cases a clean reaction was observed with a single product peak in the GC. In a preparative experiment on a 1-g scale, the hydrogenation product of **8** was isolated in > 94% yield.
[c] Determined by HPLC (see ref.[3]).
[d] R^1 = Ph, R^2 = Bn, from D-serine (see ref.[8]).
[e] 2 mL of dichloromethane, up to 2.5 mmol of substrate.
[f] Reaction time: 4 h.
[g] 3 mL of dichloromethane, 5 mmol of substrate, reaction time: 24 h.



Scheme 2. Enantioselective hydrogenation of olefins catalyzed by iridium complexes **3a – f** (see Tables 1 and 2).

methylstilbene **8**, the enantiomeric excess increased from 89% to 99% ee for the (4*S*,5*S*) complex **3a**. The *allo*-threonine-derived ligand (**3b**) was slightly less selective (97% ee), but still superior to **1**. For the β-methylcinnamic ester **9** the iridium complex **3a** (92% ee) was the most efficient catalyst, while catalyst **3b** and [Ir(COD) (**1**)] both gave 85% ee. With the cyclic substrate **10**, on the other hand, complex **3b** was the most selective catalyst (85% ee).

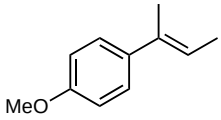
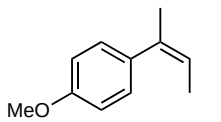
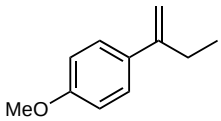
Encouraged by these results, we synthesized four additional metal complexes with different substituents (**3c – f**) and carried out further hydrogenations varying the reaction conditions. Introduction of two *meta*-methyl substituents at the R^1 group (complex **3e**) showed a further improvement in selectivity for the ester **9** (94% ee, Table 1, Entry 18).[14] Full conversion was obtained with catalyst loadings as low as 0.02 mol % (Entries 7 – 12, Table 1). For *E*-2-(4-methoxyphenyl)-but-2-ene **11**, excellent enantioselectivities (98 – 99% ee) were observed with all ligands (Table 2). The corresponding *Z*-isomer **12** gave lower enantiomeric excesses, but again catalyst **3e** (92% ee) was more selective than the serine-derived complex.

In the hydrogenation of the terminal olefin **13** similar results were obtained as with the corresponding serine-derived ligands. As previously observed,[8] the ee increases with decreasing hydrogen pressure. By lowering the temperature from 23 to 0 °C, the enantioselectivity of catalyst **3a** was raised from 84 to 89% ee. At − 78 °C virtually no conversion was observed. For this substrate, the threonine-derived catalysts offered no advantages over the serine-derived catalysts. Similar ee values in the hydrogenation of 2-arylbut-1-enes have also been reported for a DuPhos-ruthenium catalyst in the presence of *t*-BuOK (up to 89% ee)[15] and for organolanthanide catalysts (64% ee at 25 °C, 96% ee at − 78 °C).[16]

The hydrogenation of the *N*-phenylimine **14** was also briefly investigated (Table 3). With catalysts **3c** and **3f** better enantioselectivities were obtained than with the serine-derived catalysts (80 vs. 75% ee). However, these catalysts cannot compete with the best Ir-PHOX catalysts (up to 89% ee)[2] or the titanocene catalysts reported by Buchwald et al.[17] (up to 99% ee for a range of imines).

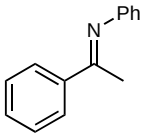
In summary, threonine-derived phosphinite-oxazolines are a useful addition to the previously reported serine-derived

Table 2. Enantioselective hydrogenation of 2-arylbutenes **11 – 13**.[a]

Entry	Substrate	Complex	*p* [bar]	*T* [°C]	Cat. loading [mol %]	Conv.[b] [%]	ee[c] [%]
1		**3a**	50	23	1	100	99 (*R*)
2		**3b**	50	23	1	100	98 (*R*)
3		**3c**	50	23	1	100	98 (*R*)
4		**3d**	50	23	1	100	98 (*R*)
5		**3e**	50	23	1	100	99 (*R*)
6		**3f**	50	23	1	100	99 (*R*)
7		**3f**	50	23	0.1	> 99	99 (*R*)
8	**11**	[Ir(COD) (**1**)][d]	50	23	0.1	100	96 (*R*)
9		**3a**	50	23	1	100	89 (*S*)
10		**3b**	50	23	1	100	88 (*S*)
11		**3c**	50	23	1	100	83 (*S*)
12		**3d**	50	23	1	100	88 (*S*)
13		**3e**	**50**	**23**	**1**	**100**	**92 (*S*)**
14		**3f**	50	23	1	100	84 (*S*)
15	**12**	[Ir(COD) (**1**)][e]	50	23	0.4	100	85 (*S*)
16		**3a**	50	23	1	100[g]	62 (*R*)
17		**3a**	1	23	1	100[g, h]	84 (*R*)
18		**3a**	1	23	0.1	100[g, h]	85 (*R*)
19		**3a**	**1**	**0**	**1**	**100[g, h]**	**89 (*R*)**
20		**3a**	1	− 78	1	< 1[g, h]	n.d.
21		**3e**	50	23	1	100[g]	66 (*R*)
22		**3e**	1	0	1	100[g, h]	86 (*R*)
23		**3f**	50	23	1	100[g]	60 (*R*)
24	**13**	**3f**	1	0	1	100[g, h]	85 (*R*)
25		[Ir(COD) (**1**)][f]	1	23	0.1	100[g]	88 (*R*)

[a] All reactions were performed using 0.1 mmol of alkene and 1 mL of dichloromethane at 50 bar of hydrogen pressure at rt (reaction time: 2 h).
[b] Determined by GC.
[c] Determined by HPLC (see ref.[3]).
[d] R^1 = ferrocenyl, R^2 = Bn (from ref.[8]).
[e] R^1 = ferrocenyl, R^2 = *i*-Pr (from ref.[8]).
[f] R^1 = 3,5-(*t*-Bu_2)C_6H_3, R^2 = Bn (from ref.[8]).
[g] Reaction time: 30 min.
[h] 3 mL of dichloromethane.

Table 3. Enantioselective hydrogenation of imine **14** with catalysts **3a – 3f**.[a]

Entry	Substrate	Catalyst	Cat. loading [mol %]	Conv.[b] [%]	ee[c] [%]
1	 **14**	**3a**	1	100	66 (*R*)
2		**3b**	1	100	53 (*R*)
3		**3c**	1	100	80 (*R*)
4		**3d**	1	100	46 (*R*)
5		**3e**	1	100	39 (*R*)
6		**3f**	1	100	80 (*R*)
7		[Ir(COD) (**1**)][d]	0.1	100	75 (*S*)

[a] All reactions were performed using 0.1 mmol of imine and 1 mL of dichloromethane at 50 bar of hydrogen pressure at rt (reaction time: 4 h).
[b] Determined by GC.
[c] Determined by HPLC on a Daicel OD-H column (*n*-heptane/2-propanol = 99: 1).
[d] R^1 = Ph, R^2 = Bn, from D-serine (see ref.[8]).

analogues and other oxazoline-based P,N-ligands. In the hydrogenation of unfunctionalized trisubstituted arylalkenes, unprecedented enantioselectivities could be obtained with these new ligands. The surprisingly strong effect of the additional methyl group in the oxazoline ring suggests that the scope of iridium-catalyzed hydrogenation can be further enhanced by variation of the substitution pattern in the oxazoline ring.

Experimental Section

(4*S*,5*S*)-2-(5-Methyl-2-phenyl-4,5-dihydrooxazol-4-yl)-1,3-diphenylpropan-2-ol (7a)

(4*S*,5*S*)-4-Methyl-2-phenyl-4,5-dihydrooxazole-4-carboxylic acid methyl ester **6**[11,12] (500 mg, 2.28 mmol) was dissolved in anhydrous diethyl ether (15 mL). Benzylmagnesium chloride solution (1 M in diethyl ether, 6.80 mL, 6.80 mmol) was added at −78 °C. The cooling bath was removed, the reaction mixture stirred for 4 h and then poured on aqueous NH_4Cl/ice (10 mL). The organic layer was washed with water (10 mL) and brine (10 mL). After drying over $MgSO_4$ the solvent was evaporated under reduced pressure. The light yellow oil was purified by column chromatography (silica gel, pentane/diethyl ether, 6:1) to afford **7a** as a white powder; yield: 690 mg (82%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.73 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 2.00 (s, 1H, O*H*), 2.69 (d, *J* = 13.6 Hz, 1H, Ph−C*H*$_2$), 2.93 (d, *J* = 13.9 Hz, 1H, Ph−C*H*$_2$), 3.11 (d, *J* = 13.9 Hz, 1H, Ph−C*H*$_2$), 3.19 (d, *J* = 13.6 Hz, 1H, Ph−C*H*$_2$), 4.11 (d, *J* = 9.6 Hz, 1H, C=N−C*H*), 4.84 (dq, *J* = 9.6 Hz, *J* = 6.8 Hz, 1H, C*H*-CH$_3$), 7.15 – 7.37 (m, 10H, CH$_2$*Ph*), 7.44 (t, *J* = 7.3 Hz, 2H, *Ph*), 7.50 (t, *J* = 7.3 Hz, 1H, *Ph*), 8.05 (d, *J* = 7.3 Hz, 2H, *Ph*).

(4*S*,5*S*)-*O*-[1-Benzyl-1-(5-methyl-2-phenyl-4,5-dihydrooxazol-4-yl)-2-phenylethyl] Diphenylphosphinite (2a)

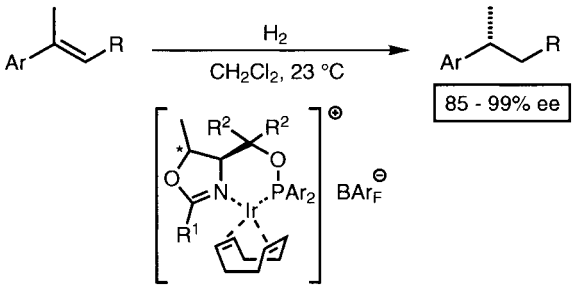
(4*S*,5*S*)-2-(5-Methyl-2-phenyl-4,5-dihydrooxazol-4-yl)-1,3-diphenylpropan-2-ol **7a** (337 mg, 0.91 mmol) was dissolved in anhydrous pentane (15 mL). At −78 °C *n*-butyllithium (0.70 mL, 1.12 mmol) was added dropwise followed by *N,N,N',N'*-tetramethylethylenediamine (0.30 mL, 2.00 mmol). The cooling bath was removed and the mixture stirred for 1 h. Chlorodiphenylphosphine (0.18 mL, 0.99 mmol) was added at 0 °C. After stirring for 5 h at room temperature the solvent volume was reduced to 0.5 mL. The residual suspension was transferred directly onto a silica gel column. Chromatography with hexane/ethyl acetate (15:1) afforded the product as a voluminous white powder; yield: 310 mg (62%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 3.11 (d, *J* = 14.1 Hz, 1H, Ph−C*H*$_2$), 3.33 (br d, *J* = 13.4 Hz, 2H, Ph−C*H*$_2$), 3.72 (d, *J* = 13.1 Hz, 1H, Ph−C*H*$_2$), 4.34 (d, *J* = 9.6 Hz, 1H, C=N−C*H*), 4.73 (m, 1H, C*H* – CH$_3$), 7.05 – 7.50 (m, 23H, CH$_2$*Ph*, *Ph*, P*Ph*$_2$), 8.01 (d, *J* = 7.3 Hz, 2H, *Ph*); ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = 88.7 (s). The product contained a small amount (ca. 1-5 mol %) of the corresponding phosphinate [^{31}P{^{1}H}-NMR: δ = 25.6]. It was used in the next step without further purification.

Complex 3a

Ligand **2a** (125 mg, 0.22 mmol) was dissolved in anhydrous dichloromethane (5 mL) under an argon atmosphere. [Ir(COD)Cl]$_2$ (83 mg, 0.12 mmol) was added and the mixture heated at reflux for 1 h. Then, with vigorous stirring, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (227 mg, 0.24 mmol) was added and, after 1 min, 3 mL of water. The layers were separated and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, dichloromethane) to give iridium complex **3a** as an orange powder; yield: 262 mg (68%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.73 (d, *J* = 7.0 Hz, 3H, C*H*$_3$), 1.75 – 2.05 [br m, 6H, C*H*$_2$(COD)], 2.05 – 2.25 [br m, 1H, C*H*$_2$(COD)], 2.27 – 2.33 [br m, 1H, C*H*$_2$(COD)], 2.95 (dd, *J* = 5.3 Hz, *J* = 14.9 Hz, 1H, Ph−C*H*$_2$), 3.04 (d, *J* = 14.4 Hz, 1H, Ph−C*H*$_2$), 3.15- – 3.38 [br m, 2H, C*H*(COD)], 3.42 (d, *J* = 14.9 Hz, 1H, Ph−C*H*$_2$), 4.10 – 4.35 [br m, 2H, Ph−C*H*$_2$ and C*H*(COD)], 4.53 [br m, 1H, C*H*(COD)], 4.75 (d, *J* = 8.1 Hz, 1H, C=N−C*H*), 5.35 (m, 1H, C*H*-CH$_3$), 6.93 (m, 2H, *Ph*), 7.08 (m, 4H, *Ph*), 7.18 (m, 2H, *Ph*), 7.23 – 7.36 (m, 7H, *Ph*), 7.51 [br s, 4H, Ar*H*(BAr$_F$)], 7.52 – 7.69 (m, 7H, *Ph*), 7.72 [m, 8H, Ar*H*(BAr$_F$)], 7.78 (m, 1H, *Ph*), 8.39 (br d, 2H, *Ph*); ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ = 93.6 (s); IR (KBr): $\tilde{\nu}$ = 3066w, 3033w, 2953w, 2926w, 1608m, 1570m, 1496w, 1452w, 1438m, 1355vs, 1281vs, 1276vs, 1131vs, 1028w, 1000m, 936m, 886m, 839m, 774m, 744s, 712s, 700s, 682m, 670m cm^{-1}. MS (FAB): 856 (M^+); anal. calcd. for $C_{77}H_{58}BF_{24}IrNO_2P$: C 53.79, H 3.40, N 0.81, O 1.86; found: C 53.74, H 3.57, N 0.68, O 2.00.

General Hydrogenation Procedure

To a 60-mL autoclave with a glass insert and a magnetic stir bar was added the substrate, the metal complex and dichloromethane (inert atmosphere is not necessary). The autoclave was sealed and pressurized with hydrogen. After stirring at room temperature for 0.5 – 24 h (see Tables) the pressure was released. The solvent was evaporated and heptane (3 mL) was added. The resulting suspension was filtered through a syringe filter (CHROMAFIL O-20/15 MS 0.2 μm, Macherey-Nagel) and the filtrate was directly analyzed by GC and chiral HPLC to determine the conversion and ee (for analytical procedures and data, see ref.[3]). In a preparative experiment on a gram scale (substrate **8**), the catalyst was removed by filtration through a short silica column (2 × 1 cm) with hexane as solvent. After evaporation of the solvent, analytically pure product was isolated in 94% yield. The hydrogenations at 1 bar were carried out using an argon-flushed open schlenk flask and a continuous slow flow of hydrogen.



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