Iridium-Catalyzed Enantioselective Hydrogenation of Terminal Alkenes

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Abstract: Iridium complexes derived from chiral P,N ligands are efficient catalysts for the enantioselective hydrogenation of 2-aryl-substituted terminal alkenes. Using 0.1–1 mol % of catalyst at room temperature and ambient hydrogen pressure, high enantioselectivities (88–94% ee), full conversions after short reaction times and essentially quantitative yields were obtained for a range of differently substituted 2-arylalkenes. Among six iridium complexes that were tested, the most selective catalyst was a complex with a phosphinite-oxazoline ligand derived from threonine (Ir-ThrePHOX). In contrast to the hydrogenation of trisubstituted alkenes, a strong pressure effect was observed for this class of substrates. Lowering the hydrogen pressure from 50 to 1 bar resulted in a strong increase of the ee values.

Keywords: alkenes; asymmetric hydrogenation; iridium; oxazolines; P,N ligands

Introduction

Iridium complexes with chiral P,N ligands are efficient catalysts for the enantioselective hydrogenation of unfunctionalized alkenes.[1,2] In this respect they clearly distinguish themselves from chiral rhodium and ruthenium catalysts, which only perform well with substrates bearing a polar coordinating group next to the C=C bond.[3–5] Extensive screening of different P,N ligands led to a set of catalysts that gave excellent enantioselectivities and high turnover numbers in the hydrogenation of various functionalized and unfunctionalized, acyclic and cyclic trisubstituted olefins.[2,6–11] Typical examples are the phosphinooxazoline (PHOX) complex **Ir-1**,[6] threonine-derived phosphinite complexes **Ir-2**, **Ir-3** and **Ir-4** (ThrePHOX),[10] the serine-derived phosphinite complex **Ir-5** (SerPHOX),[9] and the SimplePHOX complex **Ir-6**[11] (Figure 1).

With the terminal alkene **7a** (Scheme 1) only low to moderate enantioselectivities were obtained under standard conditions (20–50 bar H_2, CH_2Cl_2, 23 °C). However, the ee was found to increase strongly when the hydrogen pressure was lowered, contrasting observations with trisubstituted olefins, which showed only very small ee variations between 5 and 100 bar.[9a] In the hydrogenation of **7a** at 1 bar hydrogen pressure the ee approached 90% with Ir-SerPHOX catalysts.[9a] Only two other catalyst systems are known that give similarly high enantioselectivities. Using chiral bis(cyclopentadienyl)samarium complexes, Marks and coworkers obtained 64% ee at 25 °C and 96% ee at −78 °C in the hydrogenation of 2-phenylbut-1-ene.[12] Noyori et al.[13] examined a ruthenium complex containing Me-DuPhos as the chiral ligand in the hydrogenation of a series of 2-arylbut-2-enes **7b–g** (Scheme 1). Under basic conditions in isopropyl alcohol, containing 0.04 to 0.5 mol % of catalyst and 0.8 to 10 mol % of *t*-BuOK, the ee values ranged between 81 and 89% with conversions between 81–93%.

Based on the promising results obtained with Ir-SerPHOX catalysts, we decided to carry out a more comprehensive study on the hydrogenation of terminal olefins using the Ir catalysts shown in Figure 1.

Results and Discussion

Ir complexes **Ir-1**–**Ir-6** were tested as catalysts in the hydrogenation of seven differently substituted 2-arylbut-1-enes **7a–g** (Scheme 1). Unsubstituted 2-phenylbut-1-ene was not included in this series because no reliable analytical method for determining the ee of the product was available. To compare the influence of hydrogen pressure and temperature on the individual catalysts, three sets of reaction conditions were applied: 50 bar/23 °C, 1 bar/23 °C, 1 bar/0 °C. The high pressure reactions

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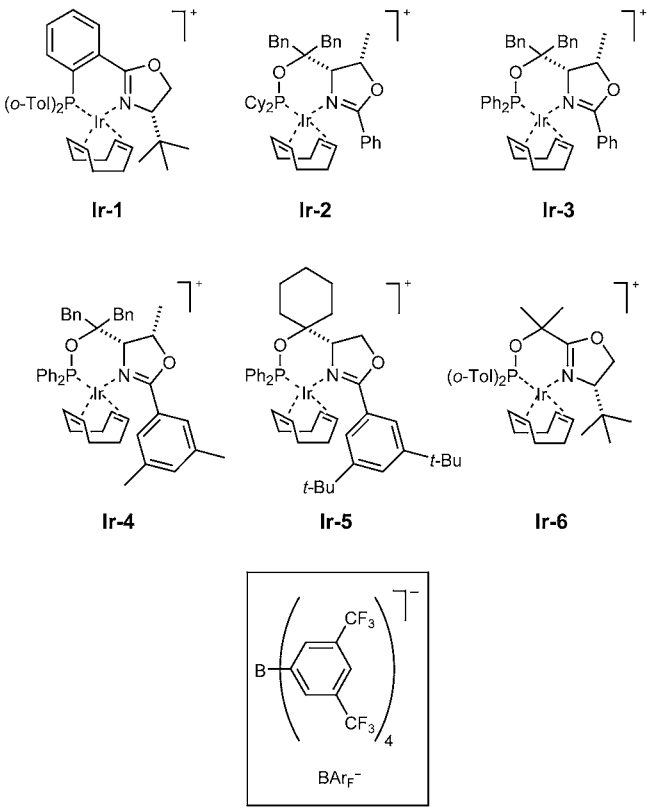
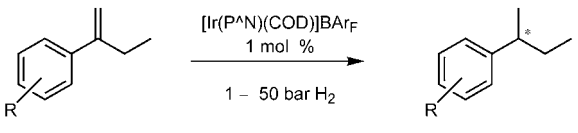


Figure 1. Iridium complexes with PHOX (**Ir-1**), ThrePHOX (**Ir-2**, **Ir-3**, **Ir-4**), SerPHOX (**Ir-5**), and SimplePHOX ligands (**Ir-6**). The counterion is BAr_F^-.

were run under standard conditions with 1 mol % of catalyst for 2 h, according to the screening protocol for trisubstituted alkenes. However, further experiments showed that full conversion can be reached within 10 min or less. To speed up the screening process, often four reactions were run in a single autoclave equipped with four glass vials, each containing a magnetic stir bar. The results proved to be reproducible and consistent with data obtained from screening reactions in separate autoclaves.

Complex **Ir-2** with a dicyclohexylphosphinite ligand from the ThrePHOX series is the most selective catalyst



7a:	R = *p*-OCH_3	**8a**
7b:	R = *p*-CH_3	**8b**
7c:	R = *p*-CF_3	**8c**
7d:	R = *p*-Cl	**8d**
7e:	R = *p*-Br	**8e**
7f:	R = *m*-Cl	**8f**
7g:	R = *m*-Br	**8g**

Scheme 1.

in the hydrogenation of substrates **7a**–**g** (Table 1). Upon lowering the hydrogen pressure from 50 bar to ambient pressure, the enantiomeric excesses increase from 54–62% to 88–94%. The highest enantioselectivity (94% ee) is obtained with the electron-rich alkene **7a**, whereas the electron-poor alkene **7c** gives only 88% ee. However, overall no clear trend reflecting electronic effects of the substituents in the aryl ring is observed. Lowering the reaction temperature to 0 °C results in a noticeable decrease of enantioselectivity, especially for substrates **7a**, **7c** and **7 g**. Thus, among the conditions tested, room temperature and ambient pressure seem to be ideal for this class of substrates.

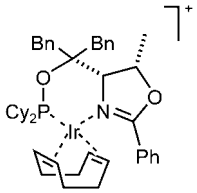
Complex **Ir-3** with a diphenyl- instead of a dicyclohexylphosphinite group is distinctly less selective, especially for alkenes **7c**–**g** (Table 2). Again, hydrogenations at 1 bar give much higher enantioselectivities than those carried out at elevated hydrogen pressure. In this case, no clear trend is observed when the temperature is lowered to 0 °C.

Figure 2 summarizes the results obtained in the hydrogenation of substrate **7a** with catalysts **Ir-1** to **Ir-6**. Additional results for substrates **7b**–**g** are listed in the Supporting Information. In all cases, the enantioselectivity increased strongly when the pressure was lowered from 50 to 1 bar. With few exceptions, higher enantiomeric excesses were observed at room temperature as compared to 0 °C. Clearly, complex **Ir-2** with a dicyclohexylphosphinite ligand is the most selective catalyst. In general, threonine-derived ThrePHOX ligands (**Ir-2**, **Ir-3, Ir-4**) and analogous serine-derived SerPHOX ligands (**Ir-5**) are better suited for this substrate class than PHOX (**Ir-1**) or SimplePHOX ligands (**Ir-6**). While for the screening experiments, 1 mol % of catalyst was used, in hydrogenations at a preparative scale the same enantioselectivity and full conversion was obtained with 0.1 mol % catalyst loading.

The common solvent for Ir-catalyzed hydrogenations is dichloromethane.[2,14] 1,2-Dichloroethane (DCE) and toluene can be used as well, whereas more strongly coordinating solvents deactivate the catalyst. Solvent effects were examined with the best catalyst for terminal alkenes, **Ir-2**, and with Ir-PHOX complex **Ir-1** using alkene **7a** as substrate (Table 3). In all three solvents the ee levels were similar. Interestingly, the enantioselectivity of catalyst **Ir-2** in DCE and toluene increased when the temperature was lowered to 0 °C, whereas the opposite trend was observed in dichloromethane. Catalyst **Ir-1** showed a more pronounced temperature effect resulting in a substantial increase of enantioselectivity when the temperature was raised from 0 °C to 25 °C. With this catalyst the ee was significantly higher in DCE than in dichloromethane. The results show that toluene is a viable alternative to halogenated solvents.

In order to accelerate catalyst screening, a protocol for simultaneous hydrogenation of a mixture of substrates in the same solution was developed.[15] Hydrogenation

Table 1. Hydrogenation of substrates **7a–g** with catalyst **Ir-2** using three different reaction conditions.

Entry	Complex[a]	Substrate	p [bar]	T [°C]	Time [min]	Conv.[b] [%]	ee[c] [%]
1		**7a**	50	25	120	>99	58
2		**7a**	1	25	30	>99	94
3		**7a**	1	0	30	>99	90
4		**7b**	50	25	120	>99	56
5		**7b**	1	25	30	>99	91
6		**7b**	1	0	30	>99	89
7		**7c**	50	25	120	>99	54
8		**7c**	1	25	30	>99	88
9	**Ir-2**	**7c**	1	0	30	>99	84
10		**7d**	50	25	120	>99	59
11		**7d**	1	25	30	>99	89
12		**7d**	1	0	30	>99	88
13		**7e**	50	25	120	>99	62
14		**7e**	1	25	30	>99	93
15		**7e**	1	0	30	>99	90
16		**7f**	50	25	120	>99	61
17		**7f**	1	25	30	>99	92
18		**7f**	1	0	30	>99	91
19		**7g**	50	25	120	>99	59
20		**7g**	1	25	30	>99	94
21		**7g**	1	0	30	>99	87

[a] 1 mol % of Ir-complex **Ir-2**. Anion: BAr_F^-.
[b] Determined by GC.
[c] Determined by HPLC (see refs.[6,7]).

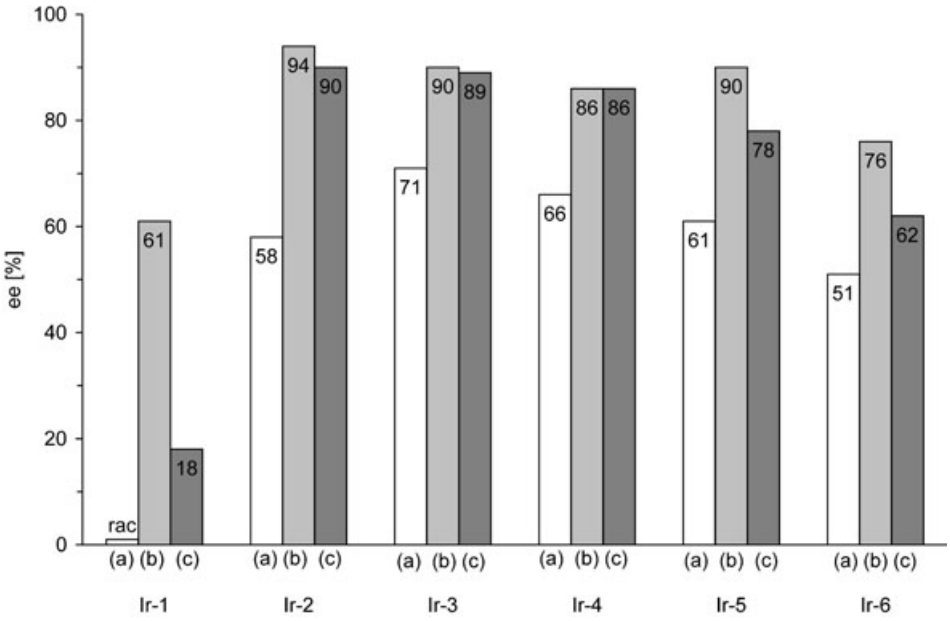


Figure 2. ee values obtained in the hydrogenation of substrate **7a** with catalysts **Ir-1** to **Ir-6**; reaction conditions: (a) 50 bar, 25 °C; (b) 1 bar, 25 °C; (c) 1 bar, 0 °C.

of an equimolar mixture of alkenes **7a**, **7c**, **7e**, and **7f** with catalyst **Ir-2** at ambient hydrogen pressure resulted in full conversion after 30 min. GC analysis of the product mixture on a chiral column showed well resolved peaks for all enantiomers of the hydrogenated products **8a**, **8c**, **8e**, and **8f** (Figure 3). Simultaneous screening of catalyst mixtures can be problematic if the different substrates or products interact with each other. However, the ee values determined from this chromatogram were identical to those obtained in reactions performed with a sin-

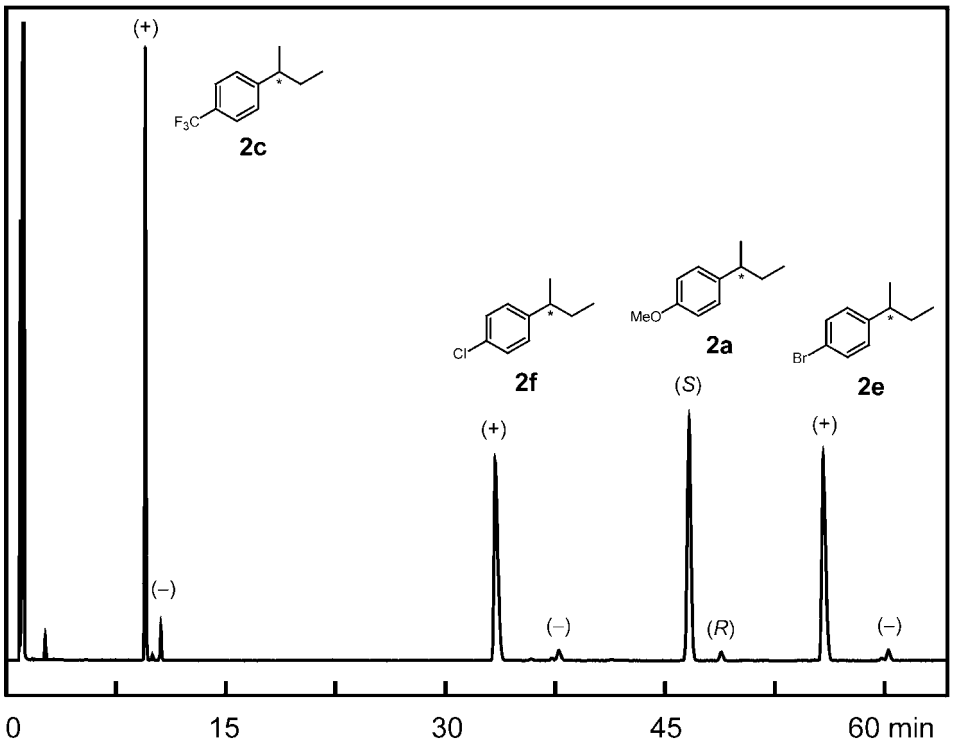
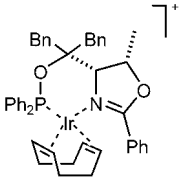


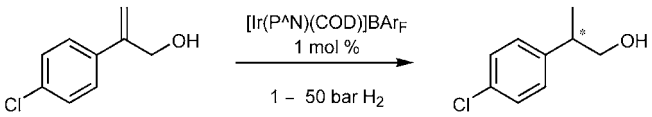
Figure 3. Determination of the ee values of products **8a**, **8c**, **8e**, and **8f** from hydrogenation of a mixture of substrates with catalyst **Ir-2**, using gas chromatography on a chiral column. Conditions: γ-CD TFA, 30 m, 100 kPa H_2, 60 °C/30 min/0.5 °C·min^{-1}/77 °C/0 min/20 °C·min^{-1}/180 °C/10 min.

Table 2. Hydrogenation of substrates **7a**–**g** with catalyst **Ir-3** using three different reaction conditions.

Entry	Complex[a]	Substrate	p [bar]	T [°C]	Time [min]	Conv.[b] [%]	ee[c] [%]
1		**7a**	50	25	60	>99	71
2		**7a**	1	25	30	>99	90
3		**7a**	1	0	30	>99	89
4		**7b**	50	25	60	>99	73
5		**7b**	1	25	30	>99	88
6		**7b**	1	0	30	>99	86
7		**7c**	50	25	60	>99	46
8		**7c**	1	25	30	>99	59
9		**7c**	1	0	30	>99	64
10		**7d**	50	25	60	>99	54
11		**7d**	1	25	30	>99	73
12		**7d**	1	0	30	>99	69
13		**7e**	50	25	60	>99	55
14		**7e**	1	25	30	>99	71
15		**7e**	1	0	30	>99	68
16		**7f**	50	25	60	>99	60
17		**7f**	1	25	30	>99	75
18		**7f**	1	0	30	>99	76
19		**7g**	50	25	60	>99	62
20		**7g**	1	25	30	>99	76
21		**7g**	1	0	30	>99	74

Ir-3

[a] 1 mol% of Ir-complex **Ir-3**. Anion: BAr_F^-.
[b] Determined by GC.
[c] Determined by HPLC (see refs.[6,7]).



9 **10**

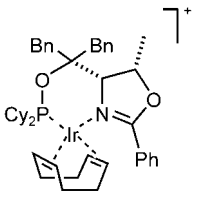
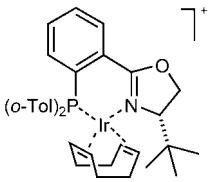
gle substrate. Obviously, the presence of additional substrates does not affect the outcome of the four individual reactions, so this protocol can be used as a fast and reliable screening method.

To examine the influence of a polar neighboring group which can coordinate to the catalyst, allylic alcohol **9** was hydrogenated using four different Ir complexes (Table 4). Derivatives of the hydrogenation product 2-phenylpropanol (**10**) are frequently used as components of fragrance mixtures.[16] Again, complex **Ir-2** proved to be the most selective catalyst, giving rise to 88% ee at 0 °C and 1 bar hydrogen pressure. Compared to unfunctionalized terminal alkenes, the pressure effect was very weak in this case (Entries 3 and 4). Interestingly, catalysts **Ir-1** and **Ir-6** gave higher enantioselectivities at higher pressure, contrasting the results obtained with alkenes **7a**–**g**. The enantiomeric excess achieved with catalyst **Ir-2** is comparable to the ee value reported for the synthesis of alcohol **10** by zirconocene-catalyzed asymmetric methylalumination of 4-chlorostyrene (90% ee).[17] However, the iridium-catalyzed hydrogenation is a more efficient, faster process requiring less catalyst.

Conclusion

Iridium complexes derived from chiral phosphinite-oxazoline ligands, especially the ThrePHOX complex **Ir-2**, are efficient catalysts for the hydrogenation of 2-

Table 3. Solvent effects on the enantioselective hydrogenation of **7a** with catalysts **Ir-1** and **Ir-2**.

Entry	Complex[a]	T [°C]	Solvent	Conv.[b] [%]	ee[c] [%]
1		0	CH_2Cl_2	>99	90
2		25	CH_2Cl_2	>99	94
3		0	$ClCH_2CH_2Cl$	>99	93
4		25	$ClCH_2CH_2Cl$	>99	91
5		40	$ClCH_2CH_2Cl$	>99	87
6		0	Toluene	>99	93
7		25	Toluene	>99	90
8	**Ir-2**	40	Toluene	>99	90
9		0	CH_2Cl_2	>99	18
10		25	CH_2Cl_2	>99	61
11		0	$ClCH_2CH_2Cl$	>99	43
12		25	$ClCH_2CH_2Cl$	>99	73
13		40	$ClCH_2CH_2Cl$	>99	76
	Ir-1				

[a] 1 mol % of Ir-complex. Anion: BAr_F^-.
[b] Reaction time = 30 min. Determined by GC.
[c] Determined by HPLC (see refs.[6,7]).

Table 4. Hydrogenation of terminal allylic alcohol **9**.

Entry	Complex[a]	p [bar]	T [°C]	Time [min]	Conv.[b] [%]	ee[c] [%]
1	**Ir-1**	50	25	120	>99	78
2	**Ir-1**	1	25	120	54	62
3	**Ir-2**	50	25	120	>99	81
4	**Ir-2**	1	25	120	>99	83
5	**Ir-2**	1	0	120	>99	88
6	**Ir-5**	50	25	120	>99	51
7	**Ir-5**	1	25	120	>99	50
8	**Ir-6**	50	25	120	>99	77
9	**Ir-6**	1	25	120	51	66

[a] 1 mol % of Ir-complex. Anion: BAr_F^-.
[b] Determined by GC.
[c] Determined by HPLC (see refs.[6,7]).

aryl-substituted terminal alkenes. With enantiomeric excesses of 88–94%, the enantioselectivities are comparable to the best values reported so far for this class of substrates. In contrast to the bis(cyclopentadienyl)samarium complex used by Marks that requires very low temperature for high enantioselectivity, Ir-catalyzed hydrogenation gives optimum results at room temperature. In addition, full conversion is obtained under neutral and mild conditions after short reaction times, whereas in the Ru-catalyzed hydrogenations developed by Noyori et al.,[13] a 20-fold excess of potassium *tert*-butoxide with respect to the catalyst was added to the reaction mixture. Moreover, the Ir complexes, used as precatalysts, are air- and moisture-stable and easy to handle. In summary, Ir-catalyzed hydrogenation provides an efficient, practical enantioselective route to chiral α-methyl-substituted benzylic compounds.

Experimental Section

Materials

Chiral ligands **1–6** and their corresponding iridium complexes **Ir-1** to **Ir-6** were prepared according to literature procedures.[6,7,9–11] Syntheses and characterization of compounds **7a–g**, **8a–g**, and **9** are described in the Supporting Information. A comprehensive documentation of catalytic results obtained with **Ir-1**, **Ir-4**, **Ir-5**, and **Ir-6** are given in Tables S1–S4 in the Supporting Information.

Screening Conditions for Catalytic Hydrogenations at Elevated Pressure

A solution of 0.1 mmol substrate and 1 mol % iridium pre-catalyst in 0.5 mL of dry dichloromethane (Fluka puriss., absolute, over molecular sieves, $H_2O = 0.005\%$) was stirred in a high-pressure autoclave under 50 bar hydrogen gas for two hours. Stirring was done with magnetic stir bars at 700 min^{-1}. All reactions were performed at room temperature. The reactions were generally set up in the air. Either one reaction was run at a time in a 35 mL glass-insert, or four reactions were run in one autoclave in 2 mL glass vials that were individually stirred. Test reactions gave consistent results with both methods and no gas-phase diffusion of the more volatile substrates from one vial to another was observed. Work-up consisted in evaporating the solvent in a stream of nitrogen or argon and extraction of the hydrogenation product with 3 mL of heptanes (HPLC quality). After filtration through a syringe filter (0.2 μm, Macherey-Nagel CHROMAFIL type O-20/15, for organic solvents), these solutions were directly used for GC and HPLC analyses.

Screening Conditions for Catalytic Hydrogenations at Ambient Pressure

A solution of 0.1–0.2 mmol substrate and 1 mol % iridium pre-catalyst in 2 mL of dry dichloromethane (Fluka puriss., absolute, over molecular sieves, $H_2O = 0.005\%$) was prepared under argon in a 15 mL Schlenk flask. The reaction mixture was stirred for 30 min with slow bubbling of hydrogen gas through the solution, introduced through a stainless-steel needle. The temperature was either 25 °C or 0 °C and kept constant by a water or ice bath. Work-up and analyses were performed as described for the high pressure reactions.

Hydrogenation on a Preparative Scale

A solution of **7a** (1.005 g, 6.19 mmol) in 60 mL of dichloromethane (0.1 M) was mixed with 0.1 mol % (10.7 mg) **Ir-2** under nitrogen. The reaction flask was connected to a gas burette and purged with hydrogen gas. Hydrogenation was then performed at ambient temperature and pressure with magnetic stirring. After 2 h, full conversion was obtained as determined by gas consumption and confirmed by GC analysis. The solvent was removed under vacuum (40 mbar/25 °C) and the crude product was purified by filtration through a silica gel column (h = 4 cm, ø = 2 cm) with 100 mL of pentane. Pentane was removed under vacuum at the same pressure and temperature to give **8a** as a colorless oil; yield: 993 mg (98%), 94% ee.

Acknowledgements

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