Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 938–944

Synthesis of an $\alpha_v\beta_3$ integrin antagonist intermediate via asymmetric hydrogenation of an α,β-unsaturated ester with BoPhoz-iridium and BoPhoz-rhodium catalysts

Antonio Zanotti-Gerosa,[a,*] William A. Kinney,[b] Gabriela A. Grasa,[c] Jonathan Medlock,[a] Andreas Seger,[a] Shyamali Ghosh,[b] Christopher A. Teleha[b] and Bruce E. Maryanoff[b]

[a]*Johnson Matthey, Catalysis and Chiral Technologies, 28 Cambridge Science Park, Cambridge CB4 0FP, UK*
[b]*Johnson & Johnson Pharmaceutical Research and Development, Welsh & McKean Roads, Spring House, PA 19477-0776, USA*
[c]*Johnson Matthey, Catalysis and Chiral Technologies, 2001 Nolte Drive, West Deptford, NJ 08051, USA*

Received 20 February 2008; accepted 31 March 2008

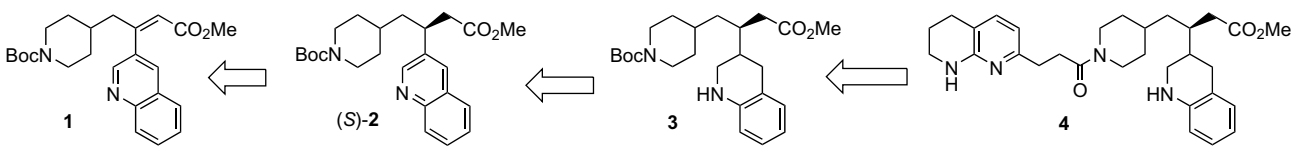
Abstract—The enantioselective synthesis of an $\alpha_v\beta_3$ integrin antagonist intermediate was approached via asymmetric hydrogenation of a β,β-disubstituted-α,β-unsaturated ester. As a result of the rapid parallel screening of a selection of ligands and catalysts, we found that neutral Me-BoPhoz-rhodium and iridium catalysts effect the required transformation with a high enantioselectivity. Both the activity and selectivity of the catalysts were strongly dependent on the choice of solvent and counter-ion. The addition of iodine modified the iridium catalyst such that the reduction of the 3-substituted quinoline ring took place.

1. Introduction

The asymmetric hydrogenation of C=C bonds is a well established methodology,[1] which has provided a cost-effective synthesis of a number of molecules of industrial relevance.[2] To develop an efficient synthetic route to an $\alpha_v\beta_3$ integrin antagonist,[3] we explored the asymmetric hydrogenation of unsaturated ester **1** to enantiomerically enriched ester (*S*)-**2**. Hydrogenation of (*S*)-**2** to tetrahydroquinoline **3** would generate the key building block for the synthesis of the target $\alpha_v\beta_3$ integrin antagonist **4** (Scheme 1).

Few relevant references are currently available for the enantioselective hydrogenation of unsaturated esters using homogeneous late transition metal catalysts. While it is known that unsaturated acids bind to the metal catalyst as carboxylate ligands prior to the coordination of the C=C bond and hydride transfer from the metal center, the mechanism of the asymmetric hydrogenation of unsaturated esters is unclear, and no general experimental procedure has been established.[4] Only a limited number of ruthenium and iridium-bisphosphine catalysts have been reported to work under different conditions on some unsaturated ester, ketones, and lactams.[5] In addition, unsaturated esters can be regarded as isolated, electron poor C=C bonds, and subjected to hydrogenation in the presence of P^N-iridium catalysts.[6]

The presence of different substituents at the β-position of the unsaturated ester and the possible existence of *E*/*Z*



Scheme 1. Retrosynthesis of **4**.

* Corresponding author. Tel.: +44 1223 225800; fax: +44 1223 438037; e-mail: antonio.zanotti-gerosa@matthey.com

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.03.031

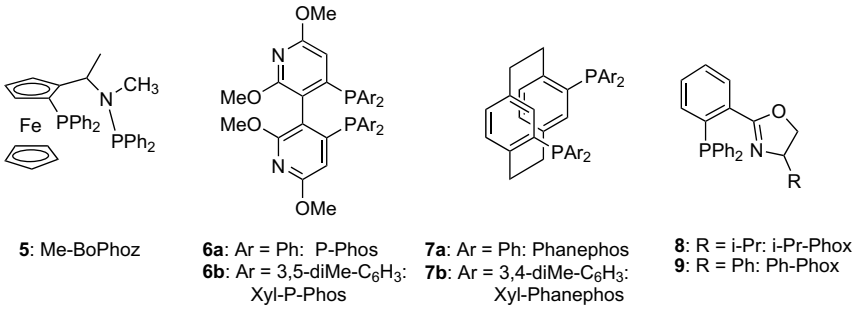


Figure 1. Ligands used in the hydrogenation screen.

isomer mixtures may, in principle, affect the enantioselective hydrogenation step. It was advantageous that, in this case, substrate **1** was available as a single *Z*-isomer.[7] The presence of a quinoline moiety in the substrate, however, introduced a further element of uncertainty since both the ester and the quinoline could competitively bind to the metal.

Faced with the challenge of a transformation for which no general effective procedure was known or available, we envisaged a broad screen of catalysts based on different metals (ruthenium, rhodium, iridium) and ligands of wide structural diversity (Fig. 1). Bo-Phoz, **5**, a mixed phosphino-aminophosphine ligand with a ferrocene backbone, has produced high activity and selectivity in asymmetric hydrogenation of C=C bonds.[8] P-Phos **6a** is the representative of the wider class of atropoisomeric phosphines and has often displayed higher activity and selectivity than the analogous BINAP ligands.[9] Phanephos **7a**, a paracyclophane-based bisphosphine, has found applications in a number of C=C and C=O asymmetric hydrogenations.[10] A selection of P^N ligands including *i*-Pr-PHOX **8** Ph-PHOX **9** was also considered (Fig. 1).

2. Results and discussion

The catalyst screen was run at relatively high catalyst loadings (substrate to catalyst molar ratio, S/C, of 50/1) and on a small scale (0.2 mmol of substrate for each reaction) using a parallel screening hydrogenation reactor Biotage Endeavor. Time constraints and substrate availability limited the number of tests that could be carried out and imposed early choices on the combinations of metal, ligand, and reaction conditions that could be pursued for further optimization.

2.1. Ruthenium catalysts

Preformed ruthenium catalysts bearing ligands of the P-Phos, Phanephos, and BoPhoz families were tested in two different solvents: methanol and 1,2-dichloroethane (DCE), at S/C 50/1, 50 °C, 25 bar of hydrogen, overnight.[11] Only limited activity was obtained, despite the relatively forced reaction conditions. As a consequence, ruthenium catalysts were abandoned at an early stage in favor of rhodium and iridium catalysts.

2.2. Rhodium catalysts

The usually highly reactive achiral catalyst DiPFc-rhodium[12] was used to produce the racemic product giving 51% conversion in MeOH at S/C 50/1, 50 °C, 25 bar of hydrogen, overnight (Table 1, entry 1). Most of the chiral cationic rhodium catalysts, which were tested under the same conditions, gave low conversion.[13] The BoPhoz-derived catalysts were prepared in situ from $[(COD)_2Rh]OTf$, as described in the literature,[8] and gave enantioselectivity ranging from 41% ee in methanol to 80% ee in THF and 90% ee in DCE (entries 3–5). Moving from cationic rhodium catalysts to neutral rhodium chloride catalysts produced a very significant increase in activity and enantioselectivity in the presence of BoPhoz catalysts (entries 6 and 7), which produced up to 95% ee. When the best catalytic system was tested at higher temperature (entry 8), the overall activity remained similar while the enantioselectivity decreased to 90% ee. Rhodium-acetylacetonate (acac) catalysts were produced in situ from both $[(acac)Rh(ethylene)_2]$ and $[(acac)Rh(CO)_2]$ and led to high enantioselectivities in the presence of Me-BoPhoz in DCE (entries 9 and 10). 2-Propanol was used as the protic

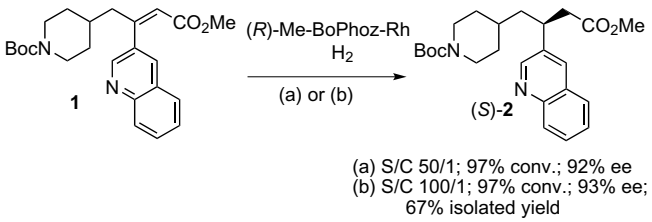
Table 1. Hydrogenation of **1** with rhodium catalysts[a]

	Catalyst	Solvent	Conv.[b] (%)	ee[b] (%)
1	[DiPFc Rh COD]BF_4	MeOH	51	—
2	[(*S*)-**7a** Rh COD]BF_4	MeOH	21	11 (*R*)
3	(*R*)-**5** + $[(COD)_2Rh]OTf$	MeOH	15	41 (*S*)
4	(*R*)-**5** + $[(COD)_2Rh]OTf$	DCE	8	90 (*S*)
5	(*R*)-**5** + $[(COD)_2Rh]OTf$	THF	10	80 (*S*)
6	(*R*)-**7a** + $[(C_2H_4)_2RhCl]_2$	DCE	58	79 (*S*)
7	(*R*)-**5** + $[(C_2H_4)_2RhCl]_2$	DCE	87	95 (*S*)
8[c]	(*R*)-**5** + $[(C_2H_4)_2RhCl]_2$	DCE	78	90 (*S*)
9	(*R*)-**5** + $[(C_2H_4)_2Rh(acac)]$	DCE	33	93 (*S*)
10	(*R*)-**5** + $[(CO)_2Rh(acac)]$	DCE	10	80 (*S*)
11	(*R*)-**5** + $[(C_2H_4)_2Rh(acac)]$	*i*-PrOH	55	68 (*S*)
12	(*R*)-**5** + $[(CO)_2Rh(acac)]$	*i*-PrOH	12	20 (*S*)
13	(*R*)-**6b** + $[(C_2H_4)_2Rh(acac)]$	DCE	13	16 (*S*)
14	(*R*)-**6b** + $[(CO)_2Rh(acac)]$	DCE	<5	—

[a] Reaction conditions: Biotage Endeavor, 0.2 mmol of substrate, 0.004 mmol of catalyst, S/C = 50/1, 3 mL of solvent, 50 °C and 25 bar of hydrogen overnight (16–18 h). COD, 1,5-cyclooctadiene; OTf, triflate; acac, acetylacetonate.

[b] By HPLC, Diacel ChiralPak AD, 0.46 × 25 cm, hexane/2-propanol (80/20), 1 mL/min, 35 °C, 210 nm.

[c] The reaction was performed at 70 °C.



Scheme 2. Reagents and conditions: (a) 0.005 mmol [Rh $(C_2H_4)_2Cl]_2$ + 0.011 mmol (*R*)-Me-BoPhoz at rt in DCE for 1 h, then 0.5 mmol substrate (0.1 M in DCE) at S/C 50/1, 60 °C, 30 bar H_2 for 16 h; (b) 0.005 mmol [Rh $(C_2H_4)_2Cl]_2$ + 0.011 mmol (R)-Me-BoPhoz at rt in DCE for 1 h, then 1 mmol substrate (0.2 M in DCE) at S/C 100/1, 60 °C, 30 bar H_2 for 60 h. Crude purified by chromatography (30% EtOAc in heptane).

solvent for comparative experiments and the activity was found to be similar to the one achievable in DCE, albeit with reduced selectivity (entries 11 and 12). The catalysts derived from [(acac)Rh(ethylene$_2$] (entries 9 and 11) and [(acac)Rh$(CO)_2$] (entries 10 and 12) gave different selectivities, suggesting that the formation of different phosphine-rhodium complexes depends on the nature of the metal precursor.

The reaction with the in situ prepared Me-BoPhoz-rhodium-chloride catalyst[14] was successfully repeated on 0.5-mmol (S/C = 50/1) or 1 mmol scale (S/C = 100/1). The reaction was conducted at 60 °C, which was a compromise between the increased activity and erosion of selectivity, to provide high conversion and 92–93% ee (Scheme 2).

2.3. Iridium catalysts

The cationic iridium catalysts [*i*-Pr–Phox Ir COD]BAr_F and [Ph-Phox Ir COD]BAr_F (Table 2, entries 1–6) were tested in various solvents. Better results were obtained in methanol rather than in DCE, with 2-propanol being intermediate in terms of activity and selectivity.[15] Conversely, the P-Phos and Xyl-P-Phos catalysts[16] gave up to 90% ee in DCE. However, these catalysts were discarded for further development because of their limited activity (entries 7–10).

The catalyst prepared in situ from (*R*)-Me-BoPhoz and [COD Ir Cl]$_2$ gave the best combination of activity and enantioselectivity in the aprotic solvents, with DCE, THF, toluene, and ethyl acetate leading consistently to high enantioselectivity (Table 2, entries 13–16). Increasing the reaction temperature from 50 °C to 70–90 °C (entries 17 and 18) resulted in a slightly higher conversion with some erosion of enantioselectivity. ^{1}H NMR analysis of the reactions showed that up to 10% of a side-product was formed (see Section 2.5). The reaction conditions of 60 °C and 30 bar were found to be the best compromise. The reaction was reproducible under such conditions at S/C = 50/1 (0.5 mmol) or S/C = 100/1 (1 mmol) (Scheme 3). The purity of the crude product by NMR was somewhat reduced with respect to that obtained in the reaction with the analogous rhodium catalyst.

Table 2. Hydrogenation of **1** with iridium catalysts[a]

	Catalyst	Solvent	Conv.[b] (%)	ee[b] (%)
1	[(*R*)-**8** Ir COD]BAr_F	MeOH	66	70 (*S*)
2	[(*R*)-**8** Ir COD]BAr_F	EtOH	30	65 (*S*)
3	[(*R*)-**8** Ir COD]BAr_F	2-PrOH	23	34 (*S*)
4	[(*R*)-**8** Ir COD]BAr_F	DCE	<5	—
5	[(*R*)-**9** Ir COD]BAr_F	MeOH	19	68 (*S*)
6	[(*R*)-**9** Ir COD]BAr_F	DCE	<5	—
7	(*S*)-**6a** + [COD Ir Cl]$_2$[c]	MeOH	5	—
8	(*S*)-**6a** + [COD Ir Cl]$_2$[c]	DCE	7	90 (*S*)
9	(*S*)-**6b** + [COD Ir Cl]$_2$[c]	MeOH	26	45 (*S*)
10	(*S*)-**6b** + [COD Ir Cl]$_2$[c]	DCE	27	90 (*S*)
11	(*R*)-**7a** + [COD Ir Cl]$_2$	DCE	<5	—
12	(*R*)-**5** + [COD Ir Cl]$_2$	MeOH	24	19 (*S*)
13	(*R*)-**5** + [COD Ir Cl]$_2$	DCE	88	95 (*S*)
14	(*R*)-**5** + [COD Ir Cl]$_2$	THF	46[d]	95 (*S*)
15	(*R*)-**5** + [COD Ir Cl]$_2$	Toluene	80[d]	91 (*S*)
16	(*R*)-**5** + [COD Ir Cl]$_2$	EtOAc	62[d]	94 (*S*)
17[e]	(*R*)-**5** + [COD Ir Cl]$_2$	DCE	90[d]	93 (*S*)
18[f]	(*R*)-**5** + [COD Ir Cl]$_2$	DCE	90[d]	92 (*S*)
19[g]	(*R*)-**5** + [COD Ir Cl]$_2$	DCE	75[h]	90 (*S*)

[a] Reaction conditions: Biotage Endeavor, 0.2 mmol of substrate, 0.004 mmol of catalyst, S/C = 50/1, 3 mL of solvent, 50 °C and 25 bar of hydrogen overnight (16–18 h). COD, 1,5-cyclooctadiene; BAr_F, tetrakis(4-fluorophenyl)borate.

[b] By HPLC, Diacel ChiralPak AD, hexane/2-propanol (80/20).

[c] The catalyst was formed from 1 equiv of [COD IrCl]$_2$ with 2.05 equiv of ligand and, after solvent evaporation, used without further purification.

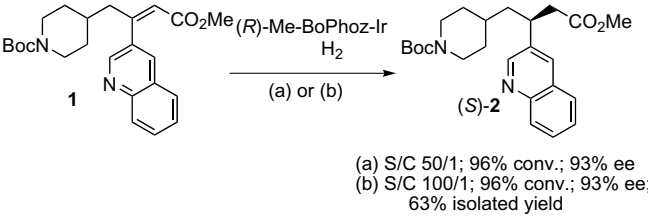
[d] Between 5% and 10% by-product was identified by ^{1}H NMR analysis of the crude.

[e] The reaction was performed at 70 °C.

[f] The reaction was performed at 90 °C.

[g] The reaction was performed at 90 °C at S/C = 100/1 and 0.25 M.

[h] ^{1}H NMR analysis showed the presence of around 10% unreacted starting material and 15% by-product.



Scheme 3. Reagents and conditions: (a) 0.005 mmol [Ir COD Cl]$_2$ + 0.011 mmol (*R*)-Me-BoPhoz at rt in DCE for 1 h, then 0.5 mmol substrate (0.1 M in DCE) at S/C 50/1, 60 °C, 30 bar H_2 for 16 h. (b) 0.005 mmol [Ir COD Cl]$_2$ + 0.011 mmol (*R*)-Me-BoPhoz at rt in DCE for 1 h, then 1 mmol substrate (0.2 M in DCE) at S/C 100/1, 60 °C, 30 bar H_2 for 60 h. Crude purified by chromatography (30% EtOAc in heptane).

2.4. Influence of added acids

In an effort to improve catalyst activity, we evaluated the addition of protic acids, which could have an influence on the reaction by preventing the coordination of the quinoline to the metal center (Table 3).[17]

The cationic [(*S*)-Phanephos Rh COD]BF_4 catalyst was chosen based on the fact that it was the most reactive chiral cationic rhodium catalyst on substrate **1**. We also found that, in the presence of acids, the activity remained modest

Table 3. Hydrogenation of **1** in the presence of acids[a]

	Catalyst	Acid (equiv)	Conv.[b] (%)	ee[b] (%)
1	[(*S*)-**7a** Rh COD]BF_4	TsOH (1)	27	67 (*R*)
2	[(*S*)-**7a** Rh COD]BF_4	TsOH (0.2)	16	77 (*R*)
3	[(*S*)-**7a** Rh COD]BF_4	AcOH (1)	13	67 (*R*)
4	[(*S*)-**7a** Rh COD]BF_4	AcOH (0.2)	14	64 (*R*)
5	[(*S*)-**7a** Rh COD]BF_4	HBF_4 (1)	37	75 (*R*)
6	[(*S*)-**7a** Rh COD]BF_4	HBF_4 (0.2)	25	85 (*R*)
7	(*S*)-**6a** + [(COD Ir Cl]$_2$[c]	HBF_4 (1)	14	80 (*S*)
8	(*S*)-**6b** + [(COD Ir Cl]$_2$[c]	HBF_4 (1)	22	83 (*S*)
9	(*R*)-**5** + [COD Ir Cl]$_2$	HBF_4 (1)	19	73 (*S*)
10[d]	(*R*)-**5** + [COD Ir Cl]$_2$	HBF_4 (1)	40	80 (*S*)
11[d]	(*R*)-**5** + [$(C_2H_4)_2$Rh Cl]$_2$	HBF_4 (1)	14	80 (*S*)

[a] Reaction conditions: Biotage Endeavor, 0.2 mmol of substrate, 0.004 mmol of catalyst, 0.2 mmol of acid, S/C = 50/1, 3 mL of MeOH, 50 °C and 25 bar of hydrogen overnight (16–18 h). COD, 1,5-cyclooctadiene.
[b] By HPLC, Diacel ChiralPak AD, hexane/2-propanol (80/20).
[c] The catalyst was formed from 1 equiv of [COD IrCl]$_2$ with 2.05 equiv of ligand, and, after solvent evaporation, used without further purification.
[d] Reactions run in DCE.

but the enantioselectivity increased significantly, in particular when sub-stoichiometric amounts of a non-coordinating acid were used in methanol (cf. Table 3, entries 1–6 and Table 1, entry 2).[18] The neutral Bo-Phoz, P-Phos, and Xyl-P-Phos-iridium catalysts displayed a similar behavior in methanol with added HBF_4 (cf. Table 3, entries 7–9 and Table 2, entries 7, 9, and 12). This behavior could be rationalized by assuming that the modest enantioselectivity in methanol in the absence of the acid is at least partially due to the co-existence of different catalytic cycles. In one of these catalytic cycles the quinoline substituent might act as the coordinating moiety and give a lower-selectivity pathway. The addition of acids may possibly shut down this pathway and favor other more selective catalytic cycle(s). Test reactions with an aprotic solvent (DCE) involving Me-BoPhoz-iridium and rhodium catalysts led to the opposite situation (cf. Table 3, entries 9–11 with Table 2, entries 12 and 13 and with Table 1, entry 8). With neutral catalysts, the addition of protic acids caused a significant degradation of both activity and selectivity. This may suggest that the higher selectivity seen in DCE is associated with the existence of a privileged catalytic pathway, possibly involving, at some stage, the coordination of the quinoline moiety to the metal.

2.5. Hydrogenation in the presence of iodine

Bisphosphine-iridium[19] and P^N-iridium[20] catalysts have recently been shown to produce, in the presence of iodine, the asymmetric hydrogenation of 2-substituted quinolines. We speculated that the side-product formed in the presence of Me-BoPhoz-iridium catalysts may be due to some over-reduction involving the quinoline ring. This hypothesis was supported by the comparison of the ^1H NMR spectra of the reactions reported in Table 2 with the NMR traces of authentic samples of **3**, which could be prepared by the hydrogenation of **2** in the presence of Pd/C.[3c]

When the reduction with the iridium catalyst was repeated on the isolated product (*S*)-**2** and in the presence of iodine,

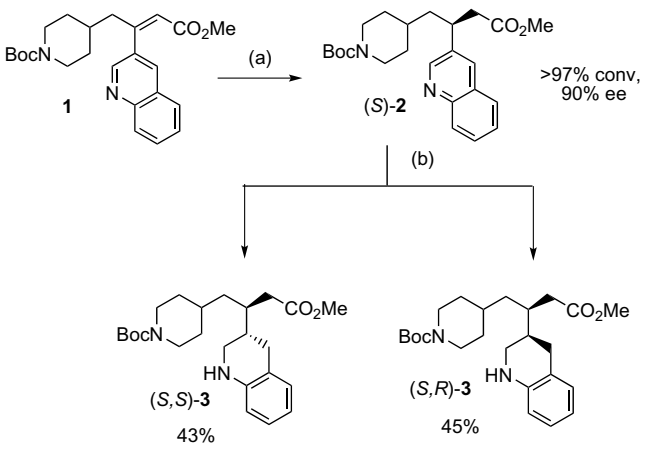
Table 4. Hydrogenation of (*S*)-**2** in the presence of iodine[a]

	Catalyst	Solvent	**2**[b] (%)	**3**[b] (%)
1	(*R*)-**5** + [COD Ir Cl]$_2$	DCE	88	12
2	(*R*)-**5** + [COD Ir Cl]$_2$	THF	17	83
3	(*R*)-**5** + [COD Ir Cl]$_2$	Toluene	58	42
4	(*R*)-**5** + [COD Ir Cl]$_2$	MeOH	92	8
5	(*R*)-**5** + [COD Ir Cl]$_2$	AcOEt	< 1	>99
6	(*S*)-**6b** + [COD Ir Cl]$_2$	AcOEt	12	88
7	(*R*)-**7b** + [COD Ir Cl]$_2$	AcOEt	76	24

[a] Reaction conditions: Endeavor, 0.2 mmol substrate (*S*)-**2**, 0.004 mmol of catalyst, 0.02 mmol of iodine, S/C = 50/1, 3 mL of solvent, 50 °C and 25 bar of hydrogen overnight (16–18 h). The ligand (0.0044 mmol) and the iridium precursor (0.002 mmol) were stirred at rt for 30 min in 1 mL of solvent prior to addition of stock solutions of the substrate and iodine. COD, 1,5-cyclooctadiene.
[b] By HPLC, Diacel ChiralPak AD-H, hexane/2-propanol (80/20).

we confirmed that BoPhoz-iridium catalysts can effectively reduce the heteroaromatic ring of the quinoline (Table 4). However, the reaction was found to be surprisingly solvent dependent. While in DCE, THF, toluene, and MeOH, the hydrogenation of the 3-substituted quinoline only occurred to a limited extent (Table 4, entries 1–4), in AcOEt the reaction took place smoothly to give two diastereoisomers of the target product, **3** (Table 4, entry 5). The reaction, however, occurred with no diastereoselectivity at the newly formed stereogenic center at the 3-position of the tetrahydroquinoline. It is notable that, under the same conditions in AcOEt, the iridium catalysts bearing the Xyl-P-Phos and Xyl-Phanephos ligands gave lower conversion than the Me-BoPhoz catalysts (entries 6 and 7).

While the Me-BoPhoz-Ir-chloride catalysts responsible for the asymmetric hydrogenation of the conjugated C=C bond were able, to a limited extent, to cause the reduction of the quinoline as a side reaction, the same catalysts could be modified in situ to produce iridium species that efficiently catalyzed the hydrogenation of the quinoline ring. By adding iodine to the hydrogenation mixture in AcOEt (without exposure to air) once the first hydrogenation step (**1** to **2**) had been completed with 90% ee at S/C = 100/1, a



Scheme 4. Hydrogenation of **1** to **3**. Reagents and conditions: (a) (*R*)-Me-BoPhoz + [COD IrCl]$_2$, S/C 100/1, AcOEt, 65 °C, 67 h, 25 bar H_2 (b) 20% I_2 added in EtOAc, 65 °C, 25 bar H_2, 24 h.

new homogeneous catalytic species was formed and **2** was further reduced to an almost equal mixture of diastereoisomers of **3** (Scheme 4). As expected from the results in Table 4, the second hydrogenation was quantitative in ethyl acetate, while it was less effective in DCE.[21]

3. Conclusions

We have approached the problem of the asymmetric hydrogenation of α,β-unsaturated ester **1** by testing a selection of ligands with significant structural diversity in combination with three different metals, ruthenium, rhodium, and iridium, and both coordinating and non-coordinating counter-ions. The results achieved so far, although not yet conducive to the development of a cost-efficient industrial process, due to the requirement for high catalyst loadings, serve to establish the BoPhoz-iridium and rhodium catalysts as effective tools for the asymmetric reduction of such unsaturated esters. Our results have also revealed some unexpected counter-ion and solvent effects in this process.

The well-established rhodium cationic hydrogenation catalysts gave limited activity and selectivity. However, the enantioselectivity could be significantly enhanced by the addition of non-coordinating acids (such as TfOH, HBF_4) in a protic solvent (MeOH).

Enantioselectivities as high as 95% ee were achieved in the presence of neutral Me-BoPhoz rhodium and iridium catalysts. The application of these classes of catalysts to asymmetric hydrogenation is unprecedented and their broader application is currently under study. The use of coordinating counter-ions (chloride, acetylacetonate) and aprotic solvents (DCE, toluene, EtOAc, THF) was found to be crucial for achieving a high enantioselectivity.

The next required synthetic step, **2** to **3**, which involves the hydrogenation of the quinoline ring, could be performed by refining the reactivity of the BoPhoz-iridium-chloride catalyst with the addition of iodine while operating in an appropriate solvent.

4. Experimental

All ligands and metal precursors are commercially available from Alfa Aesar (Johnson Matthey) or Strem Chemicals. All the reactions were run using anhydrous solvents purchased from Fluka. Substrate **1** was available as single *Z*-isomer, 95% pure by HPLC analysis (210 nm) and 85% pure by ^{1}H NMR analysis.[7] All the reactions were run in a Biotage Endeavor parallel pressure reactor (eight wells).

4.1. General procedure for the hydrogenation of 1

Procedure A (preformed catalysts): substrate **1** (0.2 mmol, 82 mg) and the catalyst (0.004 mmol) were weighed in a glass liner, placed in the Endeavor under an inert atmosphere. The solvent was added (3 mL) through the injection port, after which the reaction was purged with hydrogen five times, stirred at 800–1000 rpm, heated, and pressurized to the set values.

Procedure B (in situ catalysts): the metal precursor (0.002 mmol in the case of [COD Ir Cl]$_2$ and [$(C_2H_4)_2$ Rh Cl]$_2$ or 0.004 mmol in the case of [$(COD)_2$ Rh]OTf, [(ethylene)$_2$ Rh acac] and [$(CO)_2$ Rh acac] and the ligand (0.005 mmol) were weighed in a glass liner, placed in the Endeavor under an inert atmosphere. The solvent (1 mL) was added through the injection port and the solution was stirred under nitrogen for 30–40 min at room temperature. A solution of substrate **1** (0.2 mmol, 82 mg in 1 mL) and more solvent (1 mL) were added, the reaction was purged with hydrogen five times, stirred at 800–1000 rpm, heated, and pressurized to the set values.

The crude reaction mixtures were directly analyzed by HPLC at 210 nm on a Diacel ChiralPak AD column, 0.46 × 25 cm, eluent: hexane/2-propanol (80/20), 1 mL/min, 35 °C: starting material **1** (9.6 min), (*S*)-**2** (13.2 min), (*R*)-**2** (25.9 min).

4.2. Hydrogenation of 1 with (*R*)-Me-BoPhoz-rhodium catalyst

At first, 1.9 mg (0.005 mmol, S/C 100/1) of [$(C_2H_4)_2$ Rh Cl]$_2$ and 6.7 mg of (*R*)-Me-BoPhoz (0.0011 mmol) were weighed in a glass liner, placed in the Endeavor under an inert atmosphere. Dichloroethane (DCE, 1 mL) was added through the injection port and the solution was stirred under nitrogen for 30 min at room temperature. A solution of 410 mg of substrate **1** (1 mmol) in DCE (3 mL) was added through the injection port, followed by more DCE (1 mL) to rinse the injection port. The reaction was purged with hydrogen five times, stirred at 800–1000 rpm, heated to 60 °C, and pressurized to 30 bar of hydrogen for 60 h. The solvent was evaporated under reduced pressure. The analysis of the crude mixture by HPLC showed 97% conversion of **1** and formation of (*S*)-**2** in 93% ee. ^{1}H NMR ($CDCl_3$) showed that the product was 86% pure, which corresponded to the purity of the starting material. The crude mixture was purified by flash column chromatography on silica gel (2 cm diameter, 30–35% EtOAc in heptane) to yield 276 mg of a pale yellow oil that crystallized upon standing (67% yield). LC/MS (ES+) *m*/*z*: 413.4 (M+1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.10 (m, 1H), 7.94 (m, 1H), 7.80 (m, 1H), 7.67 (m, 1H), 7.55 (m, 1 H), 4.0 (m, 2H), 3.57 (s, 3H), 3.45 (m, 2H), 2.70 (m, 1H), 2.52 (m, 2H), 1.8 (m, 2H), 1.6 (m, 1H), 1.43 (s, 9H), 1.3–1.0 (m, 4H).[7]

4.3. Hydrogenation of 1 with (*R*)-Me-BoPhoz-iridium catalyst

The same procedure as mentioned above was used with [COD IrCl]$_2$ (3.3 mg, 0.005 mmol). The analysis of the crude mixture by HPLC showed 96% conversion to (*S*)-**2** and with 93% ee. ^{1}H NMR ($CDCl_3$) showed that the product was 74% pure. The crude mixture was purified by chromatography (30% AcOEt in heptane) to yield 258 mg of product as a white solid (63% isolated yield).

4.4. General procedure for the hydrogenation of 2 to 3

[COD Ir Cl]$_2$ (0.002 mmol) and the ligand (0.0044 mmol) were weighed in a glass liner, placed in the Endeavor under an inert atmosphere. The solvent (1 mL) was added through the injection port and the solution stirred under nitrogen for 30 min at room temperature. A solution of substrate (*S*)-**2** (0.2 mmol, 82 mg) and iodine (0.02 mmol, 5 mg) in 1 mL solvent and more solvent (1 mL) were added, the reaction purged with hydrogen five times, stirred at 800–1000 rpm, heated, and pressurized to the set values. The crude reaction mixtures were directly analyzed by HPLC at 210 nm on a Diacel ChiralPak AD-H column, 0.46 × 15 cm, eluent: hexane/2-propanol (80/20), 35 °C: **1** (5.5 min), (*S*)-**2**, (7 min), (*R*)-**2**, (10 min), (*S*,*R*)-**3** (4.6 min), (*S*,*S*)-**3** (5.6 min), (*R*,*R*)-**3** (7.1 min), (*R*,*S*)-**3** (7.3 min).

4.5. Hydrogenation of 1 to 3 with (*R*)-Me-BoPhoz-iridium catalyst

At first [COD Ir Cl]$_2$ (0.005 mmol) and (*R*)-Me-BoPhoz (0.011 mmol) were weighed in a glass liner, placed in a 50-mL Parr autoclave with magnetic stirring. The autoclave was purged with nitrogen, then AcOEt (5 mL) was added. The reaction mixture was stirred at room temperature for 1 h, then a solution of **1** (1 mmol) in AcOEt (5 mL) was added. The reaction mixture was purged five times with hydrogen, pressurized to 25 bar, and placed in an oil bath pre-heated to 65 °C. After 67 h, the reaction mixture was allowed to cool to room temperature and sampled while keeping it under a hydrogen atmosphere. HPLC analysis (AD-H, see below for conditions) showed >97% conversion to (*S*)-**2** with 90% ee. ^{1}H NMR analysis ($CDCl_3$, 400 MHz) showed full conversion to **2** with ~85% purity, consistent with the purity of starting material **1**. A solution of iodine (0.2 mmol, 50 mg) in AcOEt (3 mL) was added, the reaction purged with hydrogen, pressurized to 25 bar, and placed in an oil bath pre-heated to 65 °C. After 22 h, the reaction was stopped and the reaction solution was analyzed by HPLC at 254 nm on a Diacel ChiralPak AD-H column, 0.46 × 25 cm, eluent: hexane/2-propanol (80/20), 1 mL/min, 35 °C: **1** (10.1 min, 3%), (*S*,*R*)-**3** (8.8 min, 45%), (*S*,*S*)-**3** (10.7 min, 43%), (*S*)-**2,** (*R*,*S*)-**3** and (*R*,*R*)-**3** (co-eluted, broad, 14 min, 3%), (*R*)-**2** (21.5 min, <1%), other impurities (~5%). Integration at 254 nm was found to be in better agreement with purity by NMR analysis than integration at 210 nm. ^{1}H NMR analysis ($CDCl_3$, 400 MHz) showed full conversion to **3** with >90% purity.

References

1. (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; (b) Tang, X.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029; (c) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.
2. (a) Blaser, H. U.; Spindler, M.; Studer, M. *Appl. Catal. A* **2001**, *221*, 119; (b) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734; (c) Blaser, H. U.; Spindler, F.; Studer, M. *J. Mol. Catal. A: Chem.* **2005**, *231*, 1.
3. (a) Hutchinson, J. H.; Halczenko, W.; Brashear, K. M.; Breslin, M. J.; Coleman, P. J.; Duong, L. T.; Fernandez-Metzler, C.; Gentile, M. A.; Fisher, J. E.; Hartman, G. D.; Huff, J. R.; Kimmel, D. B.; Leu, C.-T.; Meissner, R. S.; Merkle, K.; Nagy, R.; Pennypacker, B.; Perkins, J. J.; Prueksaritanont, T.; Rodan, G. A.; Varga, S. L.; Wesolowski, G. A.; Zartman, A. E.; Rodan, S. B.; Duggan, M. E. *J. Med. Chem.* **2003**, *46*, 4790; (b) Coleman, P. J.; Brashear, K. M.; Askew, B. C.; Hutchinson, J. H.; McVean, C. A.; Duong, L. T.; Feuston, B. P.; Fernandez-Metzler, C.; Gentile, M. A.; Hartman, G. D.; Kimmel, D. B.; Leu, C.-T.; Lipfert, L.; Merkle, K.; Pennypacker, B.; Prueksaritanont, T.; Rodan, G. A.; Wesolowski, G. A.; Rodan, S. B.; Duggan, M. E. *J. Med. Chem.* **2004**, *47*, 4829; (c) Ghosh, S.; Santulli, R. J.; Kinney, W. A.; DeCorte, B. L.; Liu, L.; Lewis, J. M.; Proost, J. C.; Leo, G. C.; Masucci, J.; Hageman, W. E.; Thompson, A. S.; Chen, I.; Kawahama, R.; Tuman, W. E.; Galemmo, R. A., Jr.; Johnson, D. A.; Damiano, B. P.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5937.
4. The synthesis of **4** via asymmetric hydrogenation of an unsaturated acid intermediate has been reported elsewhere: Grasa, G.; Kinney, W. A.; Teleha, C.; Zanotti-Gerosa, A.; Ghosh, S.; Santulli, R. J.; Maryanoff, B. E., submitted for publication.
5. (a) Pousset, C.; Callens, R.; Marinetti, A.; Larcheveque, M. *Synlett* **2004**, 2766; (b) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357; (c) Yue, T. Y.; Nugent, W. A. *J. Am. Chem. Soc.* **2002**, *124*, 13693; For the asymmetric reduction of unsaturated lactams and esters in the presence of chiral copper catalysts and PMHS see: (d) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473; (e) Hugues, G.; Kimuro, H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253; (f) Jurkauskas, V.; Sadighi, J. P.; Buchwald, L. S. *Org. Lett.* **2003**, *5*, 2417.
6. (a) Pfaltz, A.; Blankestein, J.; Hilgraf, R.; Hoermann, E.; McIntyre, S.; Menges, F.; Schoenleber, M.; Smidt, S. P.; Wuestenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33; (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272; (c) Drury, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfalt, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 70.
7. Kinney, W. A.; Teleha, C.; Thompson, A. S.; Newport, M.; Hansen, R.; Ballentine, S.; Grasa, G.; Zanotti-Gerosa, A.; Ghosh, S.; Dingenen, J.; Schubert, C.; McComsey, D. F.; Leo, G.; Santulli, R. J.; Maryanoff, B. E. *J. Org. Chem.*, in press.
8. (a) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421; (b) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E.; Ponasik, J. A. *J. Org. Chem.* **2005**, *70*, 1872.
9. (a) Pai, C. C.; Lin, C. W.; Lin, C. C.; Chen, C. C.; Chan, A. S. C.; Wong, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 11513; (b) Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711.
10. Rossen, K.; Pye, P. J.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207.
11. (a) [(*S*)-P-Phos Ru Cl_2](DMF)$_n$, [(*S*)-Xyl-P-Phos Ru Cl_2](DMF)$_n$, [(*S*)-P-Phos RuCl (benzene)]Cl, [(*R*)-Xyl-P-Phos RuCl (benzene)]Cl, [(*R*)-Me-BoPhoz Cl_2](DMF)$_n$, [(*R*)-Phanephos Cl_2](DMF)$_n$ gave <10% conversion at S/C 50/1, 50 °C and 25 bar hydrogen, 16–18 h in MeOH and DCE; (b) The diphosphine-ruthenium DMF complexes were prepared as described for BINAP in: Kitamura, M.; Takunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1998**, *Coll. Vol. 9*, 589; **1993**, *Vol .71*, 1 and used without any further purification; The P-Phos-ruthenium arene complexes were prepared

according to: (c) Wu, J.; Chen, H.; Kwok, W. H.; Lam, K. H.; Zhou, Z. Y.; Yeung, C. H.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1539.
12. DiPFc = 1,1′-bis-(diisopropylphosphino)ferrocene Burk, M. J.; Harper, T. G. P.; Lee, J. R.; Kalberg, C. *Tetrahedron Lett.* **1994**, *35*, 4963.
13. Other cationic rhodium catalysts, [(diphosphine)Rh COD]-BF_4, gave <10% conversion at S/C 50/1, 50 °C and 25 bar hydrogen, 16–18 h in MeOH and DCE: (*S*,*S*)-Chiraphos, (*R*,*R*)-BDPP, (*R*,*R*)-Norphos, (*R*,*R*)-DIOP, (*S*)-Binam-P, (*R*)-CatASium, (*R*,*R*)-Et-Ferrotane, (*S*,*S*)-Me–BPE, (*R*,*R*)-Me-DuPhos, (*S*,*S*)-Spiro-P, (*S*)-P-Phos, (*R*)-Xyl-Phanephos.
14. The catalyst was preformed by stirring the metal precursor dimer (1 equiv) with the ligand (2.2 equiv) in a solvent at room temperature for 30–60 min. ^{31}P NMR analysis of the solution showed the presence of a complex mixture of products.
15. The enantioselectivity achievable in methanol with [(*R*)-*i*-Pr-Phox Ir COD] BAr_F increased slightly to 75% ee under 10 bar hydrogen and decreased to 55% ee at 70 °C.
16. (*S*)-P-Phos and (*S*)-Xyl-P-Phos, respectively, were stirred with [COD Ir Cl]$_2$ in dichloromethane at room temperature under nitrogen for 90 min. The solvent was evaporated and the crude product was used without any further purification. ^{31}P NMR (400 MHz): ^{31}P NMR (400 MHz): (*S*)-P-Phos-iridium 28 ppm (s); (*S*)-Xyl-P-Phos-iridium 28 ppm (s). The complexes were not fully characterized and their structures were tentatively assigned as [(*S*)-P-Phos Ir COD Cl] and [(*S*)-Xyl-P-Phos Ir COD Cl] by analogy with what reported in: Schneider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F. M.; Krueger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887.
17. This strategy has been applied to the synthesis of 2-pyridyl-alanine via asymmetric hydrogenation see: (a) Jones, S. W.; Palmer, C. F.; Paul, J. M.; Tiffin, P. D. *Tetrahedron Lett.* **1999**, *40*, 1211; (b) Dobler, C.; Kreuzfeld, H. J.; Michalik, M.; Krause, H. W. *Tetrahedron: Asymmetry* **1996**, *7*, 117.
18. Under the same reaction conditions of Table 4, entries 1–5, [Me–DuPhos Rh COD]BF_4 gave only 12% conversion and 10% ee.
19. (a) Wang, W. B.; Lu, S. M.; Yang, P. Y.; Han, X. W.; Zhou, Y. G. *J. Am. Chem. Soc.* **2003**, *125*, 10536; (b) Xu, L.; Lam, K. H.; Ji, J.; Wu, J.; Fan, Q. H.; Lo, W. H.; Chan, A. S. C. *Chem. Commun.* **2005**, 1390.
20. Lu, S. M.; Han, X. W.; Zhou, Y. G. *Adv. Synth. Catal.* **2004**, *346*, 909.
21. Hydrogenation of **1** to **3** in DCE: [Ir COD Cl]$_2$ + (*R*)-MeBoPhoz + **1** at S/C 50/1, 70 °C, 25 bar H_2, 24 h gave 75% conversion to (*S*)-**2** with 96% ee; after addition of iodine (10%), 70 °C, 25 bar H_2, 48 h, the reaction gave, by HPLC analysis (AD-H): 50% **2**, 16% **3** and 22% of **1**.