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Synthesis of *N*-phenyl β-amino acids via iridium-catalyzed asymmetric hydrogenation using mixed monodentate ligands

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ABSTRACT

The iridium-catalyzed asymmetric hydrogenation of *N*-phenyl-β-dehydroamino acid derivatives was examined using monodentate phosphoramidite ligands. The highest yields and enantioselectivities were obtained using a mixed ligand approach with PipPhos **L1** and achiral triphenylphosphine (full conversion, 70% ee).

1. Introduction

Enantiomerically pure β-amino acids and their derivatives not only exhibit broad biological activity but are also building blocks for the synthesis of β-peptides, β-lactam antibiotics, and other chiral pharmaceuticals.[1] Peptides containing β-amino acids show high stability toward enzymatic hydrolysis and are considered valuable as promising pharmaceutical products. In addition, β-peptides show interesting three-dimensional structures,[2] and have played an important role in advancing the understanding of enzyme mechanisms, protein conformations, and properties related to molecular recognition. As a result, the asymmetric synthesis of β-amino acids has attracted significant attention.[3]

One of the most promising methodologies, also regarding an industrial application, is the asymmetric hydrogenation of the appropriate β-dehydroamino acid precursors catalyzed by homogeneous Rh or Ru complexes containing chiral phosphine ligands.[4] Whereas the asymmetric hydrogenation of acylated α- and β-dehydroamino acids is a standard method with many industrial applications,[5] the hydrogenation of unprotected β-dehydroamino acids was developed much later. In recent years, several successful metal catalysts for the highly enantioselective asymmetric hydrogenation of β-enamino acid derivatives have been reported.[6–9] A study from the Merck/Solvias groups,[8] using deuterium labeling showed that the hydrogenation of unprotected β-dehydroamino acid derivatives proceeds through the imine tautomer.

We have developed the use of monodentate phosphoramidite ligands for the asymmetric hydrogenation of acylated α- and β-dehydroamino acids with excellent enantioselectivities.[10,11] More recently, we have reported that use of iridium complexes with phosphoramidite ligands leads to excellent results in the hydrogenation of acylated α-dehydroamino acid derivatives[12] and of C=N compounds (*N*-aryl imines, quinolines, and quinoxalines).[13]

N-Aryl β-amino acid derivatives are key structural elements of many natural products and drug intermediates.[14] One method to prepare such compounds is to perform the asymmetric hydrogenation of *N*-aryl β-enamino esters. Only a few examples of this reaction have been reported in the literature.[7,15] Therefore, we decided to examine the possibility of using Ir/phosphoramidite catalysts for the enantioselective hydrogenation of N-arylated β-enamino esters.

2. Results and discussion

Initial hydrogenation experiments were performed using 5 mol % of iridium precursor and 10 mol % of (*S*)-PipPhos **L1** ligand, at 5 bar of hydrogen pressure and room temperature, in dichloromethane (Table 1, entries 1, 2, and 8). In general rather low enantioselectivities and conversions were obtained initially. The highest ee was obtained in the hydrogenation of β-methyl *N*-phenyl enamino ester **2**, however, with low conversion (13% conversion, 36% ee, entry 2). Only 8% ee was obtained in the hydrogenation of β-phenyl substituted enamino ester **3** (46% conversion, entry 8).

Since reactions with Ir/PipPhos **L1** at 5 bar of hydrogen pressure gave modest conversions and ee's, the following experiments were performed at 25 bar of pressure. Various solvents as well as additives were screened in the asymmetric hydrogenation of β-methyl *N*-phenyl enamino ester **2** and β-phenyl *N*-phenyl enamino ester **3**. Although in solvents, such as toluene, *iso*-propanol and THF, the yield was often higher, the enantioselectivity was generally lower. The addition of I_2 led to a reduction in the enantioselectivity. The reaction in DCM led to the highest enantioselectivity.

Over the last decade, both Reetz et al.[9,16] and ourselves[17,18] have shown that the use of mixtures of chiral monodentate ligands can improve both the enantioselectivity and the reactivity in asymmetric

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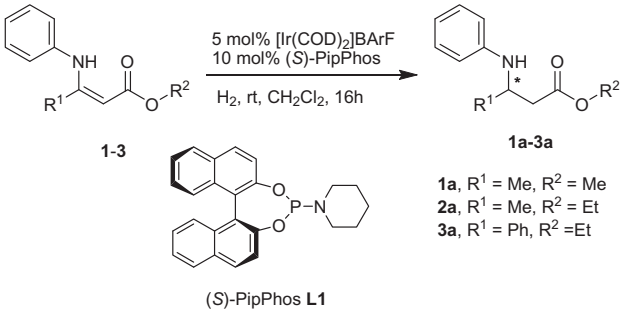
Table 1
Asymmetric hydrogenation of *N*-phenyl β-enamino esters using [Ir(COD)$_2$]BArF/(*S*)-PipPhos **L1**[a]



Entry	Prod.	Solvent	P (bar)	Conv.[b] (%)	ee[c] (%)
1	**1a**	DCM	5	21	20
2	**2a**	DCM	5	13	36
3		DCM	25	45	25
4		Toluene	25	73	16
5		IPA	25	98	5
6		THF		99	2
7[d]		THF	25	100	3
8	**3a**	DCM	5	46	8
9		DCM	25	34	20
10		Toluene	25	47	17
11		IPA	25	48	9
12		THF	25	73	20
13[d]		THF	25	43	0

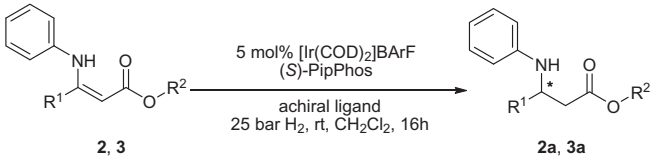
[a] Reaction conditions: 100 μmol enamino ester, 5 μmol [Ir(COD)$_2$]BArF, 10 μmol (*S*)-PipPhos, 2.55 mL of solvent, CH_2Cl_2, 5 or 25 bar H_2, 16 h.
[b] Conversion was determined by GC.
[c] Enantiomeric excess was determined by HPLC.
[d] 10 mol % I_2.

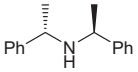
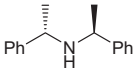
hydrogenation reactions. It is also possible to use mixed complexes based on a monodentate chiral ligand and a non-chiral phosphorus ligand. Therefore, we decided to examine the possibility of using a mixture of phosphoramidites with achiral P-ligands or amines. Reactions were performed using 5 mol % of [Ir(COD)$_2$]BArF and (*S*)-PipPhos **L1** as a ligand, at 25 bar of hydrogen pressure and room temperature. When an achiral phosphine was used as a second ligand, the ratio between PipPhos **L1** and achiral ligand was 2/1. This was to prevent the formation of [Rh(PPh$_3$)$_2$(COD)] as this complex is capable of very fast hydrogenation and leads to a racemic product. In the reactions where an amine was used as the second ligand, the ratio of ligands was PipPhos L1/amine = 1:1, as in the case of Crabtree's catalyst.[19] The results of the hydrogenation of substrates **2** and **3** are presented in Table 2.

The addition of amine ligands, (*S*,*S*)-2-phenyl-1-(1-phenylethyl)-propylamine or triethylamine (entries 2, 3, 7, and 8) resulted in excellent conversions, but no enantioselectivity was observed with either substrate; When achiral phosphines were added in combination with (chiral) PipPhos, the highest ee was achieved using triphenylphosphine in the hydrogenation of both **2** and **3** (up to 65% ee, entries 4 and 9). In the case of substrate **3**, the conversion was somewhat lower (54%, entry 9). Since the PipPhos/PPh$_3$ mixture induced the highest enantioselectivity in the hydrogenation of *N*-phenyl β-enamino esters, we decided to perform this reaction at a higher concentration (1 mmol scale, 4 mL of solvent) and lower catalyst loading, on substrate **1**. Various achiral P-ligands were tested in combination with PipPhos **L1**. The results are shown in Table 3.

Reactions were performed at 25 bar of hydrogen pressure and room temperature, using 1 mol % of [Ir(COD)$_2$]BArF, 2 mol % of PipPhos **L1** and 1 mol % of achiral ligand, in dichloromethane. The best result was again obtained using triphenylphosphine in combination with PipPhos **L1**, providing full conversion and 70% ee (entry 1). With the use of tri-*o*-tolylphosphine **L3** no conversion was

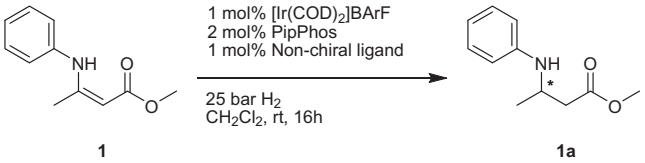
Table 2
Asymmetric hydrogenation of enamines using Ir catalysts with mixed ligands[a]



Entry	Prod.	Achiral ligand	Ir/L*/L	Conv.[b] (%)	ee[c] (%)
1	**2a**	–	1/2/0	45	25
2		Et_3N	1/1/1	100	0
3			1/1/1	94	0
4		PPh_3	1/2/1	100	65
5		$(2\text{-}MeC_6H_4)_3P$	1/2/1	48	16
6	**3a**	–	1/2/0	34	20
7		Et_3N	1/1/1	100	2
8			1/1/1	100	0
9		PPh_3	1/2/1	54	45
10		$(2\text{-}MeC_6H_4)_3P$	1/2/1	15	5

[a] Reaction conditions: 100 μmol substrate, 5 μmol [Ir(COD)$_2$]BArF, 10 μmol (*S*)-PipPhos **L1**, 2.55 mL of CH_2Cl_2 rt, 25 bar H_2, 16 h.
[b] Conversion was determined by GC.
[c] Enantiomeric excess was determined by HPLC.

Table 3
Achiral ligands screened in the asymmetric hydrogenation of **1**[a]



1 **1a**

Entry	Achiral ligand		Conv.[b] (%)	ee[c] (%)
1	PPh_3	**L2**	100	70
2	$(2\text{-}MeC_6H_4)_3P$	**L3**	0	—
3	$(3\text{-}MeC_6H_4)_3P$	**L4**	100	52
4	$(2,4,6\text{-}MeC_6H_2)_3P$	**L4**	5	—
5	$(4\text{-}MeOC_6H_4)_3P$	**L5**	100	63
6	$(Naphth\text{-}1\text{-}yl)_3P$	**L6**	29	42
7	$(t\text{-}Bu)_3P$	**L7**	6	nd
8	$(MeO)_3P$	**L8**	100	47
9	Ph_3PO	**L9**	42	40
10	$(Me_2N)_3PO$	**L10**	26	38

[a] Reaction conditions: 1 mmol **1**, 0.01 mmol $[Ir(COD)_2]BArF$, 0.02 mmol (*S*)-PipPhos **L1**, 0.01 mmol achiral ligand, 4 mL of DCM, rt, 25 bar H_2, 20 h.
[b] Conversion was determined by ^1H NMR.
[c] Enantiomeric excess was determined by HPLC.

obtained, while the use of other phosphines with a substituent at the *ortho*-position also led to low conversions (**L4** and **L6**, entries 4 and 6). Use of the bulky phosphine **L7** led to low conversion (6%, entry 7). Full conversions and ee's up to 63% were achieved using phosphines with substituents at the *meta*- or *para*-positions (entries 3 and 5). These results suggest that *o*-substituted achiral phosphines as well as the bulky phosphine **L7** are perhaps too sterically demanding for coordination to the iridium together with the PipPhos **L1** ligand. When trimethylphosphite **L8** was used with PipPhos **L1**, full conversion was accomplished (47% ee), whereas with addition of triphenylphosphine oxide **L9** only up to 42% conversion and 40% ee was achieved; the addition of HMPA only led to a slight improvement (entries 8–10).

In addition to the achiral ligand screening, we examined the use of four different phosphoramidite ligands in combination with triphenylphosphine **L2** in the hydrogenation of **1**. The reactions were performed using 1 mol % of iridium precursor, 2 mol % of phosphoramidite ligand, and 1 mol % of triphenylphosphine, at 25 bar of hydrogen pressure and room temperature, in dichloromethane. The results are presented in Table 4. Unfortunately, all the ligands employed induced low conversions. The highest enantioselectivity accompanied by very low conversion was obtained using phosphoramidite **L13** in combination with triphenylphosphine (entry 4, 8% conversion, 46% ee).

3. Conclusion

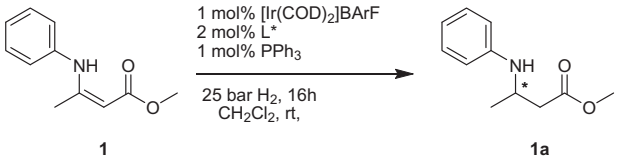
In conclusion, we have examined various in situ prepared iridium catalysts in the hydrogenation of β-dehydroamino acid derivatives. The highest enantioselectivity was obtained in a mixed ligand approach using a mixture of the chiral phosphoramidite ligand PipPhos **L1** and achiral triphenylphosphine **L2** (full conversion, 70% ee).

4. Experimental

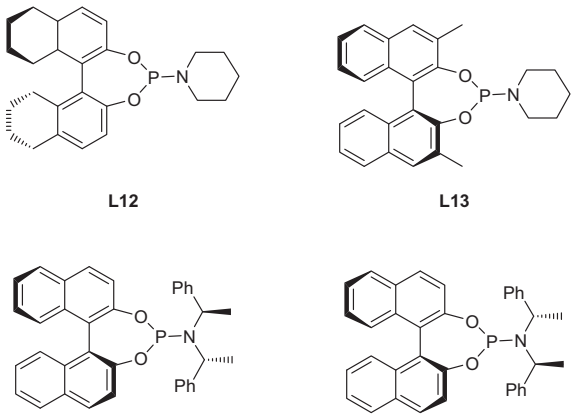
4.1. General remarks

All solvents were reagent grade and were dried and distilled, if necessary, following standard procedures. Reagents were purchased from Aldrich, Acros, Merck, or Fluka and used as received.

Table 4
Screening of phosphoramidite ligands in the asymmetric hydrogenation of **1**[a]



1 **1a**



L12 **L13**

(*S*,*R*,*R*)-**L14** (*S*,*S*,*S*)-**L15**

Entry	Ligand	PPh_3	Conv.[b] (%)	ee[c] (%)
1	**L12**	–	19	6
2	**L12**	+	7	nd
3	**L13**	–	4	nd
4	**L13**	+	8	46
5	**L14**	–	11	10
6	**L14**	+	11	0
7	**L15**	–	20	3
8	**L15**	+	20	6

[a] Reaction conditions: 1 mmol **1**, 0.01 mmol $[Ir(COD)_2]BArF$, 0.02 mmol L*, 0.01 mmol PPh_3, 4 mL of DCM, rt, 25 bar H_2, 16 h.
[b] Conversion was determined by ^1H NMR.
[c] Enantiomeric excess was determined by HPLC.

$[Ir(COD)_2]BArF$ was obtained from Umicore and used as such. NMR spectra were obtained on Varian Gemini-200 and Varian AMX400 spectrometers. GC analysis was carried out on HP6890 using a flame ionization detector, while HPLC analysis was performed on Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. The enantiomeric excess was determined by HPLC with chiral columns (Chiralcel OD and AS-H), in comparison with racemic products. Racemic products were prepared by the Pd/C catalyzed hydrogenation of enamino-esters. High resolution mass spectra were recorded on an AEI-MS-902 mass spectrometer.

Reactions were performed in a stainless steal autoclave containing seven glass vessels (8 mL volume). These vessels were closed with septum caps. Magnetic stir bars were placed inside of each vessel and the needles were placed through the septa in order to enable entrance of hydrogen. Vessels were filled under air and then flushed with nitrogen before hydrogen pressure was applied.

Ligands **L1**,[20] **L12**,[10c] **L13**,[21] **L14**,[20] and **L15**[20] were prepared according to literature procedures.

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