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Iridium-Catalysed Asymmetric Hydrogenation of Enamides in the Presence of 3,3′-Substituted H8-Phosphoramidites

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Abstract: *In situ* generated iridium complexes containing bulky 3,3′-substituted H8-phosphoramidites as ligands catalyse the asymmetric hydrogenation of non-functionalised enamides in high yield and good to excellent selectivity.

Keywords: asymmetric catalysis; enamides; hydrogenation; iridium; phosphoramidite ligands

Introduction

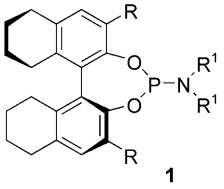
Asymmetric hydrogenation constitutes an important method for the economic and environmentally benign formation of chiral centres. In the last decades numerous catalytic systems based on precious metal complexes have been developed for the effective and highly enantioselective hydrogenation of various olefin classes. Typically, Rh and Ru complexes are used, which require coordinating groups, such as carbonyl, adjacent to the double bonds to direct their activity and to achieve high enantioselectivity. In contrast to that, mainly Pfaltz and co-workers have shown in their elegant work that Ir catalysts can be used successfully in the hydrogenation of non-functionalised olefins.[1] More recently, also examples of selective and active catalysts based on iridium have been used in the hydrogenation of acetamido esters. In detail, de Vries et al.[2] described the use of iridium complexes with bulky phosphoramidites to hydrogenate acetamidocinnamate with up to 98% *ee*. Soon after, our group used novel 3,3′-disubstituted H8-binaphthophosphoramidites which achieved excellent results in the hydrogenation of α-and β-amino acid precursors.[3,4] In order to demonstrate the relevance of the new catalytic system, further investigations on a more broad scope of functionalised alkenes, such as β-amino acid precursors, were performed. Given our experience in the hydrogenation of aryl-enamides[5] and their attractive potential to form chiral amines, they were selected as subject of our further investigations. Since the original work of Kagan,[6] a number of studies on the Rh- or Ru-catalysed asymmetric hydrogenation of arylenamides has been published. While in the beginning research mainly has been focused on the design of chelating phosphorus ligands like Me-DuPhos, Me-BPE, DIOP, BINAP, and others[6,7] an increasing number of monodentate P ligands was successfully applied in this area.[5,8]

In this work, we report on the successful use of sterically demanding phosphoramidite ligands **1** in the iridium-mediated hydrogenation of several aryl- and alkyl-enamides. A thorough study on the influence of additives to the catalytic system has been conducted with remarkable consequences on the activity and enantioselectivity of the system.

Results and Discussion

So far only two studies on the hydrogenation of simple enamides by iridium catalysts are known.[9] At best moderate enantioselectivities of up to 60% *ee* have been reported for an iridium complex containing a mixed phosphine olefin ligand.[10]

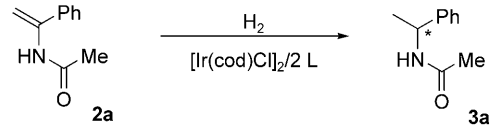
As model reaction, the hydrogenation of *N*-(1-phenylvinyl)acetamide **2a** in the presence of phosphoramidites **1** was chosen (Scheme 1). The catalytic ex-



1a: R = H; $R^1 = CH_3$
1b: R = Br; $R^1 = CH_3$
1c: R = 4-CH_3O-C_6H_4; $R^1 = CH_3$
1d: R = C_6H_5; $R^1 = CH_3$
1e: R = 2-naphthyl; $R^1 = CH_3$
1f: R = 2,4,6-$(CH_3)_3C_6H_2$; $R^1 = CH_3$
1g: R = 4-F-C_6H_4; $R^1 = CH_3$

Scheme 1. Monodentate 3,3′-substituted phosphoramidites **1** based on H8-binaphthol.

Table 1. Hydrogenation of *N*-(1-phenylvinyl)acetamide **2a**.[a]



Entry	Ligand	Conv. [%]	*ee* [%]
1	**1a**	14	–
2	**1b**	27	18 (*S*)
3	**1c**	>99	**84** (*S*)
4	**1d**	85	56 (*S*)
5	**1e**	>99	78 (*S*)
6	**1f**	60	44 (*S*)
7	**1g**	>99	82 (*S*)

[a] All reactions were carried out at 10 °C under 10 bar pressure of hydrogen for 16 h with 2.5 μmol $[Ir(cod)Cl]_2$, 5 μmol ligand and 0.25 mmol substrate in 2.0 mL toluene.

periments were performed in an 8-fold parallel reactor array with a reactor volume of 3.0 mL.[11] Initial investigation on the effect of the variation of the ligand substituents immediately gave a remarkable outcome (Table 1). In fact, under typical conditions (2 mol% of $[Ir(cod)Cl]_2$ as catalyst precursor and 4 mol% ligand in toluene at 10 °C, 10 bar of hydrogen for 16 h) ligands **1a–g** showed significantly different behaviours. Ligand **1a** lacking substitution in 3,3′-positions does not form an active catalytic species (Table 1, entry 1).

On the other hand substitution with the *p*-methoxyphenyl, naphthyl or *p*-fluorophenyl group induced full conversion within 16 h and good enantioselectivity of up to 84%. Peculiarly, the more basic mesityl-substituted ligand **1f**, which has been used with best success in the reduction of acetocinnamates,[3] gave here poor performance concerning both activity and enantioselectivity of the catalyst. Bromide ligand **1b** is not active as previously reported, while the simple phenyl-substituted **1d** is moderately active but far less enantioselective than its parent aryl-substituted ligands **1c**, **1e** and **1g**. Notably, a beneficial effect of the 3,3′-disubstitution on enantioselectivity has also been reported with BINAP ligands in the asymmetric hydrogenation of *N*-(1-phenylvinyl)acetamide.[12]

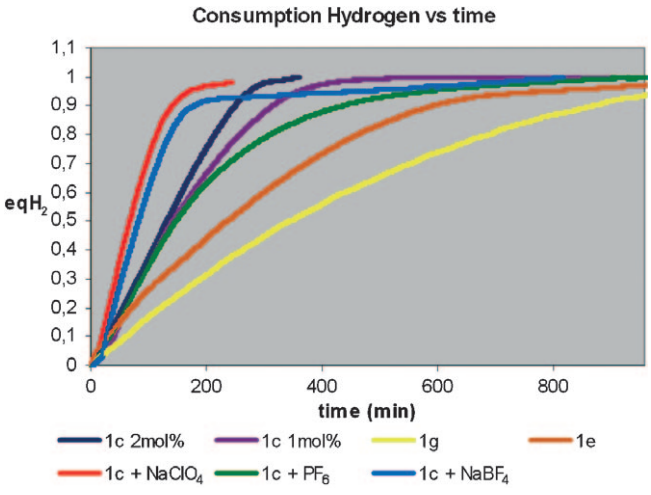
From the results shown, it was not clear whether the active system was still a monodentate iridium-phosphoramidite complex. However, reactions with two equivalents of ligand did not show any increase in enantioselectivity. Nevertheless, a thorough investigation on the effect of additives was conducted. A representative list of sodium salts added to $[Ir(cod)Cl]_2$/**1c** is reported in Table 2. It is known from the works of Crabtree[13] and Pfalz[14] that iridium complexes can form active dimeric complexes. Thus, the addition of a non-coordinating anion, which might stabilise the more selective monomeric form, is often advantageous. Several anionic salts were tested such as $NaPF_6$, $NaClO_4$, $NaBF_4$, $NaBAr_F$, etc. We were pleased to find that many of these salts induce an improvement of the enantioselectivity (Table 2, entries 5–7). Especially, the addition of $NaClO_4$ induced a remarkable increase of enantioselectivity of up to 93% *ee*. Worthy of note is the scarce activity of the BAr_F-modified system, which has been active in other hydrogenations reported by Pfaltz.[15]

Table 2. Effect of the addition of anionic salts (NaX).[a]

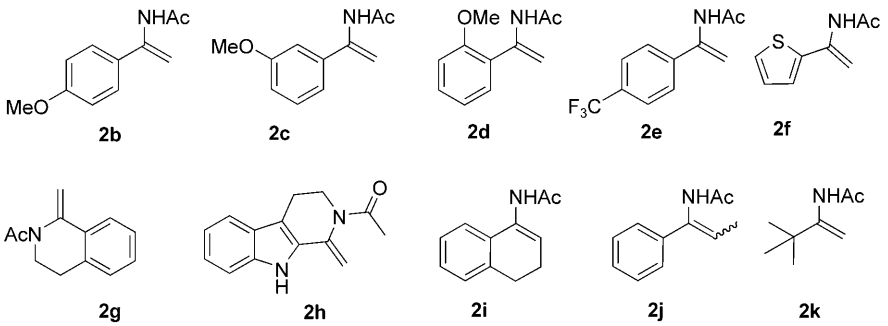
Entry	Additive	Conv. [%]	*ee* [%] (*S*)
1	NaCOOH	>99	90
2	Na_2SO_4	>99	88
3	SDS	>99	87
4	I_2	90	2
5	$NaBF_4$	>99	91
6	$NaClO_4$	>99	**93**
7	$NaPF_6$	>99	92
8	$NaBAr_F$	65	68

[a] Reactions were carried out at 10 °C under 10 bar pressure of hydrogen for 16 h with 2.5 μmol $[Ir(cod)Cl]_2$, 5 μmol ligand **1c**, 5 μmol NaX or I_2 and 0.25 mmol substrate in 2.0 mL toluene. $NaBAr_F$ = sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, SDS = sodium dodecyl sulfate.

Next, a more detailed study on the kinetics of the reaction was conducted at normal pressure and 25 °C (Scheme 2). Here, we monitored closely the activity of the reduction with different catalyst loadings.[16] Among the highly enantioselective ligands, the *p*MeO-phenyl-substituted phosphoramidite **1c** presented the highest TOF. Notably, the addition of salts like $NaClO_4$ or $NaBF_4$ improves the catalytic activity (average TOF estimated from the consumption curve: 22 h^{-1}). An observable improvement in activity is re-



Scheme 2. Hydrogen consumption *versus* time at different reaction conditions.



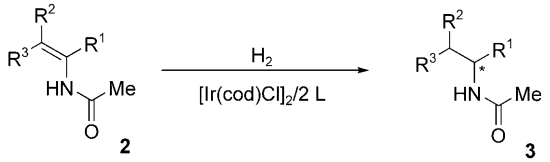
Scheme 3. Selection of synthesised aryl- and alkyl-enamides **2b–k**.

corded also after reduction of the catalyst loading to 1 mol% (average TOF: 21 h^{-1} *vs.* 11 h^{-1}).

Finally, the catalyst system modified with $NaClO_4$ was tested on a broader selection of enamides. The different α-aryl-enamides **2i, 2j** and **2k** were synthesised according to literature procedures by reduction of the corresponding oximes with iron powder in the presence of acetic anhydride.[17] Enamide substrates **2a**–**2f** were prepared using a modified synthetic protocol starting from the corresponding nitrile.[5a,18] The enamides **2g** and **2h** were synthesised according to the described procedure (*vide infra*) by acylation of, respectively, 2-phenylethylamine or tryptamine with neat acetic anhydride, subsequent ring formation *via* Bischler–Napieralski-reaction in the presence of P_2O_5,[19] and finally double bond shift to the exocyclic position by acetylation of the imine with acetic anhydride.[5b,20,21]

The different aryl- and alkyl-enamides **2** (Scheme 3) were subjected to hydrogenation using 2 mol% of $[Ir(cod)Cl]_2$/**1c** as catalyst adding 2 mol% $NaClO_4$ (Table 3). Among the enamides **2b–d** bearing a methoxy group on different positions of the phenyl ring, the highest enantioselectivity is detected for *para*-substitution (Table 3, entries 1, 2 and 5). Further attempts to improve the catalyst activity by changing the additive (Table 3, entries 3, 8, 13 and 16) or reducing the catalyst loading (Table 3, entries 4 and 10) did not improve the outcome of the reaction. Interestingly, even the alkyl-substituted enamide **2k** gave a comparatively high enantioselectivity of up to 73% *ee* (Table 3, entry 18).

Table 3. Hydrogenation of aryl- and alkyl-enamides.[a]



Entry	Substrate	Conv. [%]	*ee* [%]
1	**2b**	>99	**88** (*S*)
2	**2c**	78	81 (*S*)
3[b]	**2c**	35	81 (*S*)
4[c]	**2c**	>99	82 (*S*)
5	**2d**	21	64 (*S*)
6	**2e**	99	70 (*S*)
7	**2f**	52	49 (−)
8[b]	**2f**	44	64 (−)
9	**2g**	>99	15 (−)
10[c]	**2h**	99	17 (+)
11	**2h**	90	12 (+)
12	**2i**	17	60 (−)
13[b]	**2i**	18	51 (−)
14	**2j** (6/5)[d]	>99	7 (−)
15	**2j** (9/1)[d]	58	29 (−)
16[b]	**2j** (9/1)[d]	96	14 (−)
17	**2k**	>99	70 (+)
18[b]	**2k**	>99	73 (+)

[a] Reactions were carried out at 10 °C under 10 bar pressure of hydrogen for 16 h with 2.5 μmol $[Ir(cod)Cl]_2$, 5 μmol ligand **1c**, 5 μmol $NaClO_4$ and 0.25 mmol substrate in 2.0 mL toluene.
[b] + 5 μmol $NaBF_4$.
[c] Iridium:enamide = 1:100.
[d] Enamide **2j** was synthesised and used in different *E/Z* ratios as given in parentheses.

Conclusions

In situ generated iridium complexes of bulky H8-binaphthophosphoramidites **1** are active and highly enantioselective catalysts for the hydrogenation of non-functionalised enamides. The catalyst system is sensitive to the addition of non-coordinating salts ($NaClO_4$, $NaBF_4$, etc.). Under optimised conditions a number of aryl-substituted enamides as well as sterically hindered alkyl-enamides are selectively reduced.

Experimental Section

All manipulations were performed under an argon atmosphere using standard Schlenk techniques. Toluene was dis-

tilled from sodium benzophenone ketyl under argon. $[Ir(cod)Cl]_2$ (purchased by STREM) was stored under argon. Sodium salts were all commercially available and used without further manipulations. Enamides **2a–k** were synthesised following the literature procedures mentioned above.

Iridium-Catalysed Hydrogenation

In a standard experiment, an 8-fold parallel autoclave equipped with a magnetic stirring bar was filled with substrate (0.25 mmol), $[Ir(cod)Cl]_2$ (1 mol%), ligand **1** (2 mol%) and $NaClO_4$ (2 mol%) dissolved in toluene (2 mL). The reaction was set up under an argon atmosphere. The autoclave was pressurised to 10 bar with H_2 and the solution stirred at 10 °C for 16 h. The pressure was released and the solvent was evaporated. The residue was taken up in EtOH and the solution was directly analysed by HPLC to determine the conversion and the enantioselectivity.

2a: *ee*s were determined by HPLC (ChiralPak AD-H): (*R*)-**3a** 6.6 min and (*S*)-**3a** 8.8 min (eluent: *n*-heptane/ethanol 95:5; flow: 1.0 mL min^{-1}).

2b: *ee*s were determined by HPLC (ChiralPak AD-H): (*R*)-**3b** 20.3 min and (*S*)-**3b** 29.5 min (eluent: *n*-heptane/ethanol 98:2; flow: 1.5 mL min^{-1}).

2c: *ee*s were determined by HPLC (ChiralPak AD-H): (*R*)-**3c** 30.6 min and (*S*)-**3c** 33.6 min, (eluent: *n*-heptane/ethanol 95:5; flow: 1.0 mL min^{-1}).

2d: *ee*s were determined by HPLC (ChiralPak AD-H): (*R*)-**3d** 11.4 min and (*S*)-**3d** 17.3 min (eluent: *n*-heptane/ethanol 95:5; flow: 1.0 mL min^{-1}).

2e: *ee*s were determined by HPLC (ChiralPak AD-H): (*S*)-**3e** 12.7 min and (*R*)-**3e** 16.9 min (eluent: *n*-heptane/ethanol 95:5; flow: 0.8 mL min^{-1}).

2f: *ee*s were determined by HPLC (Chiralcel OD-H): (−)-**3f** 27.0 min and (+)-**3f** 32.4 min (eluent: *n*-heptane/ethanol 98:2; flow: 1.0 mL min^{-1}).

2g: *ee*s were determined by HPLC (ChiralPak-AD-H): (−)-**3g** 11.0 min and (+)-**3g** 13.7 min (eluent: *n*-heptane/ethanol 95:5; flow: 1.0 mL min^{-1}).

2h: *ee*s were determined by HPLC (Chiracel OJ-H): (+)-**3h** 37.5 min and (−)-**3h** 46.9 min (eluent: *n*-hexane/ethanol 95:5; flow: 1.0 mL min^{-1}).

2i: *ee*s were determined by HPLC (Chiralpak AD-H): (−)-**3i** 8.2 min and (+)-**3i** 9.2 min (eluent: *n*-heptane/ethanol 95:5, flow: 1 mL min^{-1}).

2j: *ee*s were determined by HPLC (Chiralcel OJ-H): (+)-**3j** 11.9 min and (−)-**3j** 13.6 min (eluent: heptan/ethanol 95:5, flow: 1 mL min^{-1}).

2k: *ee*s of **3k** were determined by GC (Lipodex E 25 m): (+)-**3k** 49.0 min, (−)-**3k** 50.4 min.

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