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Homogeneous Hydrogenation of Tri- and Tetrasubstituted Olefins: Comparison of Iridium-Phospinooxazoline [Ir-PHOX] Complexes and Crabtree Catalysts with Hexafluorophosphate (PF_6) and Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F) as Counterions

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Abstract: Four iridium complexes with achiral phosphino-oxazoline (PHOX) ligands were readily prepared in two steps starting from commercially available phenyloxazolines. The air-stable complexes with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F) as counterion showed high reactivity in the hydrogenation of a range of tri- and tetrasubstituted olefins. The best results were obtained with an iridium complex (**11**) derived from a dicyclohexylphosphino-oxazoline ligand bearing no additional substituents in the oxazoline ring. With several substrates, which gave only low conversion with the Crabtree catalyst, $[Ir(Py)(PCy_3)(COD)]PF_6$, full conversion was observed. The productivity of the Crabtree catalyst could be strongly increased by replacing the hexafluorophosphate anion with tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. In one case, in the hydrogenation of a tetraalkyl-substituted C=C bond, $[Ir(Py)(PCy_3)(COD)]BAr_F$ gave higher conversion than catalyst **11**. However, with several other substrates complex **11** proved to be superior.

Keywords: Crabtree catalyst; homogeneous catalysis; hydrogenation; iridium; N,P ligands

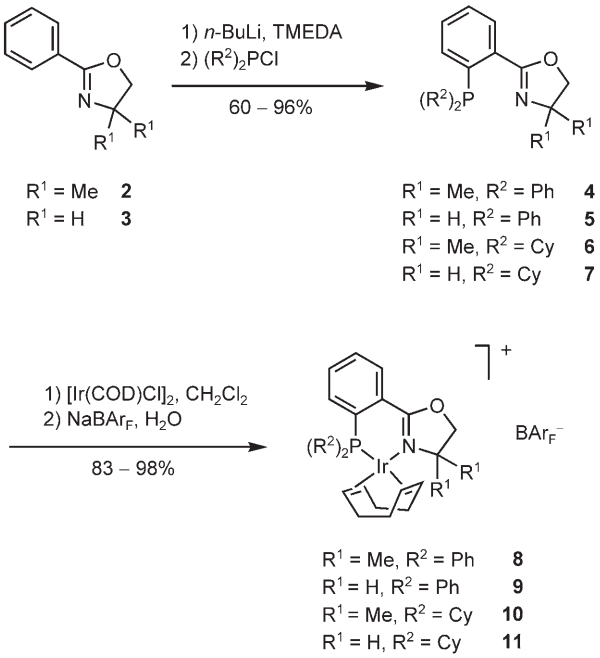
Introduction

Homogeneous hydrogenation of tri- and tetrasubstituted alkenes is often difficult.[1] Most catalysts give only low or no conversion, unless a polar group, which can speed up the reaction by coordination to the catalyst, is present near the C=C bond. The Crabtree catalyst $[Ir(Py)(PCy_3)(COD)]PF_6$ (**1**) is a notable exception, showing high activity in the hydrogenation of unfunctionalized tri- and even tetrasubstituted alkenes.[2] However, with hindered alkenes conversion is often only moderate due to deactivation of the catalyst during the reaction.

In the course of our work on the asymmetric iridium-catalyzed hydrogenation of olefins[3] we observed that iridium catalysts derived from phosphino-oxazoline (PHOX) ligands in many cases gave higher conversion than the Crabtree catalyst. The difference was particularly striking for trisubstitued alkenes bearing heteroaromatic substituents. We also found that catalyst deactivation strongly depends on the nature of the counterion. Ir-PHOX complexes with the very weakly coordinating BAr_F anion {BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate} proved to be much more resistant to deactivation and significantly less moisture sensitive than the corresponding hexafluorophosphate salts.[3,4] Based on these findings, we thought that simple achiral Ir-PHOX complexes as well as the BAr_F analogue of the Crabtree catalyst would be synthetically useful catalysts, especially for the hydrogenation of unreactive highly substituted olefins. Here we report the preparation of four achiral, easily accessible Ir-PHOX complexes and a comparative evaluation of these catalysts together with the Crabtree catalyst and its BAr_F analogue in the hydrogenation of tri- and tetrasubstituted olefins.

Results and Discussion

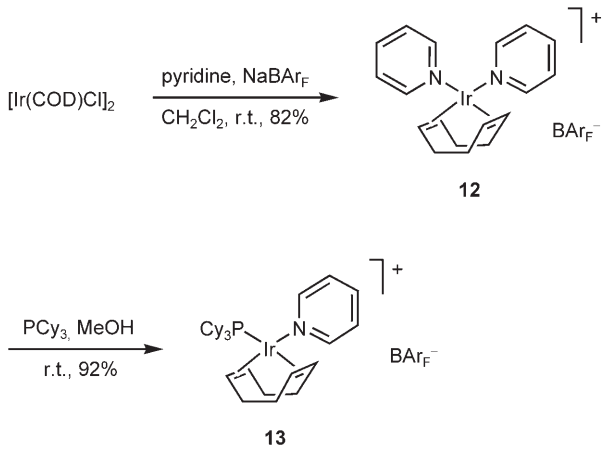
ortho-Lithiation of the commercially available oxazolines **2** and **3** and subsequent reaction with diphenyl- or dicyclohexylchlorophosphine provided the desired phosphino-oxazolines **4–7** in high yields. Complexation of these ligands with $[Ir(COD)Cl]_2$ followed by anion exchange with $NaBAr_F$[5] in a two-phase dichloromethane/water system led to the desired iridium complexes **8–11** in 83–98% yield (Scheme 1).[6]



Scheme 1. Synthesis of Ir-PHOX complexes **8–11**.

To study the influence of the anion of the Crabtree catalyst $[Ir(Py)(PCy_3)(COD)]PF_6$ (**1**), the analogous BAr_F salt **13** was prepared.[7] Attempts to obtain complex **13** directly from commercially available Crabtree catalyst by anion exchange were unsuccessful. Therefore, the route used by Crabtree[8] for the synthesis of the corresponding hexafluorophosphate **1** was chosen (Scheme 2). By a modified procedure, starting from $[Ir(COD)Cl]_2$, pyridine and $NaBAr_F$, the bis(pyridine) complex **12** was readily obtained. Stirring of complex **12** in the presence of a slight excess of tricyclohexylphosphine in methanol led to the desired product **13**, which was isolated in 75% overall yield based on $[Ir(COD)Cl]_2$ after recrystallization from diethyl ether.

Ir-PHOX complexes **8–11**, the Crabtree catalyst (**1**) and the analogous BAr_F salt **13** were tested as catalysts in the hydrogenation of a range of tri- and tetrasubstituted olefins, including alkenes bearing furyl, thienyl and pyrrolyl groups (Table 1).[9] All reactions were carried out with 1 mol% iridium catalyst at room temperature in CH_2Cl_2 under 50 bar hydrogen



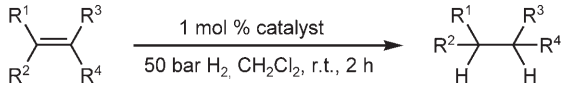
Scheme 2. Synthesis of iridium complex **13**.

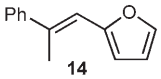
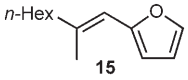
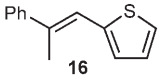
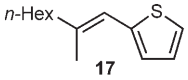
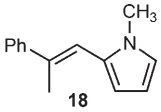
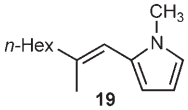
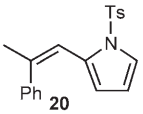
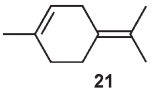
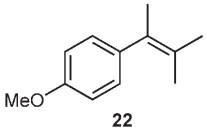
pressure for 2 h. For substrates **14–20** and **22** hydrogenation of the double bond occurs cleanly without formation of by-products whereas for substrate **21** mixtures of mono- and bis-hydrogenated products were observed. In this case the conversions listed in Table 1 refer to the formation of fully hydrogenated product.

Among the four Ir-PHOX derivatives **8–11**, complex **11** with a dicyclohexylphosphino group and no additional substituents in the oxazoline ring proved to be the most reactive catalyst, giving full conversion with all substrates except **21** (Entry 8). Heterogeneous catalysts such as palladium on charcoal also gave high conversion with furan derivatives **14** and **15**, but produced numerous by-products due to hydrogenation of the furan and benzene rings. As can be seen from the results, steric hindrance in the oxazoline ring reduces the reactivity of the catalyst (compare **8** *vs.* **9** and **10** *vs.* **11**), whereas an electron-rich dialkyl-substituted phosphorus atom has a beneficial effect compared to a diphenylphosphino group (**11** *vs.* **9**, **10** *vs.* **8**).

Comparison of the Crabtree catalyst (**1**) with the BAr_F analogue **13** clearly shows the strong influence of the counterion. In several cases, full conversion was achieved with complex **13** whereas the Crabtree catalyst was deactivated before the reaction reached completion. The BAr_F anion also strongly reduces the oxygen and moisture sensitivity of the complex. While reactions with the hexafluorophosphate salt **1** had to be set up under inert atmosphere, the BAr_F analogue **13** and Ir-PHOX complexes **8–11** could be handled in air. Overall, the BAr_F salt **13** is a more efficient catalyst than the corresponding hexafluorophosphate **1**, although, in the hydrogenation of the less reactive aromatic substrates **14**, **18**, **20**, and **22**, it suffers as well from deactivation. In these cases the Ir-PHOX catalyst **11** is clearly superior, especially for the very unreactive 1-pyrrolyl-2-phenylalkene **20** and the tetrasubstituted anisyl-alkene **22**. Substrate **21** containing a tetra-alkyl substituted C=C bond is a no-

Table 1. Ir-catalyzed hydrogenation of tri- and tetrasubstituted olefins with different Ir catalysts.



Entry	Substrates	Conversion [%]					
		8	**9**	**10**	**11**	**1**[b]	**13**
1[a]	 **14**	49	>99	>99	>99	16	91
2[a]	 **15**	10	>99	>99	>99	>99	>99
3[a]	 **16**	28	>99	88	>99	31	>99
4[a]	 **17**	31	>99	91	>99	>99	>99
5[a]	 **18**	1	5	27	>99	2	6
6[a]	 **19**	1	>99	32	>99	>99	>99
7[c]	 **20**	6	94	68	>99	27	73
8[a,d]	 **21**	17 (2.8:1 *dr*)	10 (2.3:1 *dr*)	41 (1.3:1 *dr*)	61 (2.6:1 *dr*)	61 (6.0:1 *dr*)	>99 (4.0:1 *dr*)
9[a]	 **22**	0	68	0	>99	0	8

[a] Conversions were determined by GC (Restek Rtx-1701).
[b] Reactions using catalyst **1** were set up in a glove box under nitrogen atmosphere.
[c] Conversions were determined by GC (Optima-5-Amin).
[d] Conversion to the fully hydrogenated product. Diastereomeric ratios are given in brackets; the major isomer was the *cis* compound according to published ^{13}C NMR data (ref.[10]).

table exception. Here, the BAr_F analogue of the Crabtree catalyst was the only complex found that gave full conversion. With this substrate all catalysts reacted with moderate diastereoselectivity in favour of the *cis* product.

Conclusions

In summary, we have shown that the structurally simple Ir-PHOX complex **11** is a highly efficient, convenient catalyst for the hydrogenation of tri- and tetrasubstituted olefins. The complex is readily prepared in two steps from commercially available starting materials and is easy to handle due to its air and moisture stability. In several cases, this complex proved to be clearly superior to the Crabtree catalyst or heterogeneous hydrogenation catalysts. In addition, we have found that replacement of the hexafluorophosphate anion of the Crabtree catalyst by BAr_F results in higher catalytic activity and higher stability against oxygen and moisture. The BAr_F analogue **13** proved to be a particularly efficient catalyst for the hydrogenation of substrate **21** with a tetra-alkyl substituted C=C bond. Our results indicate that complexes **11** and **13** offer a practically useful alternative to the

Crabtree catalyst for the hydrogenation of unreactive olefins.

Experimental Section

Analytical data of compounds **4–13**: see Supporting Information

General Procedure for the Synthesis of PHOX Ligands 4–7

Oxazoline **2** or **3** (**2**: 95 mg, **3**: 80 mg, 0.54 mmol) was dissolved in anhydrous pentane (8 mL) under an argon atmosphere. Anhydrous *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (90 μL, 0.59 mmol) was added dropwise and the solution was cooled using an acetone/dry ice cooling bath. At −78 °C *sec*-butyllithium solution (1.3 M in cyclohexane; 0.45 mL, 0.59 mmol) was added slowly *via* syringe. After stirring for another 15 min, the cooling bath was removed, the orange solution stirred at room temperature for 10 min and cooled again to −78 °C. After 5 min chlorodiphenylphosphine (0.11 mL, 0.70 mmol) or chlorodicyclohexylphosphine (0.16 mL, 0.70 mmol), respectively, was added dropwise. The yellow reaction mixture was warmed to room temperature overnight and evaporated under high vacuum. The crude products **4–6** were purified by column chromatography (see Supporting Information); product **7** was used for the synthesis of complex **11** without further purification.

General Procedure for the Synthesis of Ir-PHOX-Complexes 8 and 9

Ligand **4** or **5** (**4**: 65 mg, **5**: 61 mg, 0.18 mmol) was dissolved in anhydrous dichloromethane (2 mL) under an argon atmosphere. To the stirred solution $[Ir(COD)Cl]_2$ (61 mg, 0.09 mmol) was added and the dark red solution was refluxed for 2.5 h. After cooling to room temperature, $NaBAr_F$ (170 mg, 0.18 mmol) was added and the mixture was stirred for another 10 min before dilution with water (4 mL). After vigorous stirring for 30 min the layers were separated and the aqueous layer was extracted twice with dichloromethane (2×5 mL). The combined organic layers were washed with water (5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the resulting red solid purified by column chromatography (see Supporting Information).

General Procedure for the Synthesis of Ir-PHOX-Complexes 10 and 11

To a red solution of $[Ir(COD)Cl]_2$ (134 mg, 0.20 mmol) in anhydrous dichloromethane (2 mL) under argon, a solution of the appropriate ligand (**6**: 150 mg, **7**: 137 mg, 0.40 mmol) in anhydrous dichloromethane (10 mL) was added dropwise over 15 min. After stirring the reaction mixture for 1 h at room temperature, first $NaBAr_F$ (189 mg, 0.20 mmol) and 10 min later water (10 mL) were added. The two layers were stirred vigorously for 30 min. After separation of the layers, the aqueous layer was extracted twice with dichloromethane (10 mL). The combined red organic layers were washed with water (10 mL) and brine (10 mL) and dried over Na_2SO_4. After evaporation of the solvents under reduced pressure a red residue was obtained, which was purified by column chromatography (see Supporting Information).

Synthesis of $[Ir(Py)_2(COD)]BAr_F$ (12)

$[Ir(COD)Cl]_2$ (420 mg, 0.62 mmol) was dissolved in anhydrous dichloromethane (20 mL) under argon atmosphere. Upon dropwise addition of anhydrous pyridine (stored over molecular sieves; 0.7 mL, 8.7 mmol) the red solution turned yellow. Then $NaBAr_F$ (1.20 g, 1.35 mmol) was added and the reaction mixture was stirred at room temperature overnight. After filtration under an argon atmosphere, the solvent and the excess of pyridine were evaporated in high vacuum. The yellow residue was dissolved in diethyl ether and filtered twice, in order to remove residual $NaBAr_F$. The resulting yellow solid was dried under high vacuum and used for the synthesis of iridium complex **13** without further purification; yield: 1.51 g (82 %).

Synthesis of $[Ir(Py)(PCy_3)(COD)]BAr_F$ (13)

$[Ir(Py)_2(COD)]BAr_F$ (**12**) (677 mg, 0.5 mmol) was transferred into a flame-dried 50-mL Schlenk flask in a glove box and dissolved in degassed anhydrous methanol (20 mL). To the resulting yellow solution tricyclohexylphosphine (170 mg, 0.6 mmol) was added portionwise under an argon atmosphere. The solution was stirred at room temperature for 30 min and during this time an orange precipitate formed. The solvent was removed under high vacuum and the residue was precipitated from a mixture of anhydrous diethyl ether (3 mL) and anhydrous pentane (30 mL), filtered under argon atmosphere and dried under high vacuum. The crude product was purified by crystallization from anhydrous diethyl ether; yield: 714 mg (92 %).

Iridium-Catalyzed Hydrogenation

A glass-lined 60-mL autoclave equipped with a magnetic stir bar was filled with substrate (0.1 mmol) and iridium catalyst (1 mol %) dissolved in dichloromethane (0.5 mL). In case of the BAr_F salts **8–11** and **13** the reaction was set up in air, whereas with the Crabtree catalyst (**1**) the solution was prepared in a glove box under a nitrogen atmosphere. The autoclave was pressurized to 50 bar with H_2 and the solution stirred at room temperature for 2 h. The pressure was released slowly and the solvent was evaporated. The residue was taken up in hexanes (3 mL) and the mixture stirred for another 10 min prior to filtration through a syringe filter (Chromafil O-20/15 MS 0.2 μm, Macherey–Nagel). The filtrate was directly analyzed by GC to determine the conversion. GC conditions: Carlo Erba HRGC Mega 2 Series MFC 800; split-injector 1:20; FID-detector; sample amount: 1 μL; columns: a) Restek Rtx-1701, 14 %-cyanopropylphenyl-86 %-dimethylpolysiloxane (30 m, 0.25 mm, 0.25 μm); carrier gas: He (60 kPa); temperature program: 100 °C (2 min), 7 °C min^{-1}, 250 °C (10 min) or b) Optima-5-Amin (30 m, 0.25 mm, 0.5 μm), carrier gas: He (100 kPa), temperature program: 60 °C (3 min), 10 °C min^{-1}, 270 °C (15 min).

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