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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 3947–3950

Unusual base dependent enantioselectivity in a transfer hydrogenation using axially chiral Ir(III)-catalysts

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Received 12 October 2005; accepted 1 November 2005
Available online 23 November 2005

Abstract—New bidentate monosulfonated diamines, with an axially chiral biaryl backbone in combination with different Ir(III) complexes, were investigated in the catalytic transfer hydrogenation of acetophenone under *i*-PrOH/*i*-PrOK conditions. The resulting catalysts showed a strong, unexpected, and unusual base dependent enantioselectivity. Less base than chiral catalyst resulted in an (*R*)-configured secondary alcohol, excess of base in the (*S*)-enantiomer, using (*P*)-configured ligands.

1. Introduction

Asymmetric transfer hydrogenation of prochiral ketones is one of the best methods of obtaining enantiomerically enriched secondary alcohols and excellent enantioselectivities have been achieved.[1] For this transformation, Ru,[2–8] Rh, and Ir[9–13] derived chiral catalysts have been used extensively. To probe the mechanistic pathways of transfer hydrogenation reactions, experimental, and computational studies have been performed mainly with Ru(II)[14–19] and Ir(I) complexes.[20] However to the best of our knowledge, Ir(III) complexes have not been used. In general, it remains a formidable challenge because the key intermediates often have a very short lifetime.

Following our synthesis of various axially chiral ligands with a biaryl backbone,[21–23] we became interested in more active catalysts for transfer hydrogenation reactions. We observed in our experiments with acetophenone as substrate, that the catalyst activity could be improved upon by increasing the flexibility of the ligand around the metal. This was achieved by attaching aminomethylene groups at the two peri positions of the biaryl backbone (Fig. 1). Furthermore, one could modify these methylene groups at a later time to tune the ligand properties.

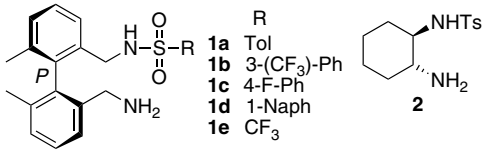

Figure 1. New, monosulfonated axially chiral biaryl diamine ligands **1a–e** and the known ligand **2**.

Surprisingly, we observed that the stereochemical outcome was greatly influenced by the quantity of base, which is unprecedented in the literature.

2. Results and discussion

2.1. Transfer hydrogenation of acetophenone in *i*-PrOH

A screen of different metal complexes in combination with our ligands (Fig. 1) in the catalytic transfer hydrogenation of acetophenone in *i*-PrOH revealed Ir(III) to be the superior metal cation (Table 1). The catalysts were all prepared in situ because they could not be obtained in a crystalline and pure form. Purified material always resulted in a very low activity. The best conversion was achieved with the complex $[IrCp^*Cl(\mu\text{-}H)]_2$ (entry 3),[24] which, to the best of our knowledge, has never been used in transfer hydrogenation reactions. The complex $[IrCp^*Cl_2]_2$ (entry 2) gave inferior conversion although it is probably the most common Ir(III)-source for this type of reaction. Interestingly, $[IrCp^*Cl(\mu\text{-}H)]_2$

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doi:10.1016/j.tetasy.2005.11.002

Table 1. Transfer hydrogenation of acetophenone in *i*-PrOH (0.1 M)

Entry	Metal complex[a]	30 min[b]		2 h		Config
		Conv (%)	ee (%)	Conv (%)	ee (%)	
1	$[Ru(cymene)Cl_2]_2$	6	35	10	38	*R*
2	$[RhCp^*Cl_2]_2$			20	2	*R*
3	$[IrCp^*Cl_2]_2$	29	39	42	40	*R*
4	$[IrCp^*Cl(\mu\text{-}H)]_2$	65	20	75	19	*S*
5	$\{[IrCp^*]_2(\mu\text{-}H)_3\}PF_6$	5[c]	1	9	17	*S*
6	$[IrCp^*Br_2]_2$	19	32	32	34	*R*
7	$[IrCp^*_2]BF_4$	3	23	12	28	*S*

Acetophenone/(*P*)-**1a**/metal/*i*-PrOK = 100:1.1:1:2.
[a] $[Rh(COD)Cl]_2$ and $[Ir(COD)Cl]_2$ gave less than 2% conversion; $[RhCp^*Cl_2]_2$ led to racemic product.
[b] Conversion and ee determined by GC.
[c] $\{[IrCp^*]_2(\mu\text{-}H)_3\}PF_6$ as well as the Cl-salt were not completely soluble in the reaction mixture, even after refluxing for 30 min.

Table 2. Transfer hydrogenation of acetophenone at 23 °C (100 mM in *i*-PrOH) using ligands **1a**–**e** and **2**

Entry	Ligand	*i*-PrOK (equiv)	10 min[a]		2 h		Config
			Conv (%)	ee (%)	Conv (%)	ee (%)	
1	**1a**	0.6	35	59	72	57	*R*
2		1	61	54	88	53	*R*
3		10	46	43	84	46	*S*
4	**1b**	0.6	38	72	56	69	*R*
5		1	67	67	92	65	*R*
6		10	45	39	83	48	*S*
7	**1c**	0.6	19	63	52	62	*R*
8		1	66	63	95	61	*R*
9		10	40	37	79	48	*S*
10	**1d**	0.6	21	53	55	52	*R*
11		1	55	54	93	53	*R*
12		10	45	44	86	49	*S*
13	**1e**[b]	0.6	18	82	33	82	*R*
14		1	10	42	23	55	*R*
15		10	38	46	93	47	*S*
16	**2**	1	2	16	6	72[c]	*R*
17		10	3	28	9	74[d]	*R*

Acetophenone/ligand/$[IrCp^*Cl(\mu\text{-}H)]_2$/*i*-PrOK = 100:1.1:0.5:0.6, 1, or 10.
[a] Conversion and ee determined by GC.
[b] 1.0 equiv ligand used.
[c] After 71 h: 78% conv 95% ee (*R*).
[d] After 23 h: 59% conv 90% ee (*R*).

gave (*S*)-1-phenylethanol in 20% ee whereas $[IrCp^*Cl_2]_2$ gave the (*R*)-configured product in 39% ee.

We next examined the behavior of ligands **1a**–**e** (Fig. 1) in the catalytic reduction of acetophenone with 0.6, 1, or 10 equiv of *i*-PrOK (Table 2). In general, ligands **1a**–**e** exhibited high activities during the first minutes of the reaction, which then dropped significantly regardless of the concentration of acetophenone present at that time.

The highest obtained TOF_{50} of 402 h^{-1} for **1b** (entry 5) was in the range of the reported TOF_{50} values from 120 to 450 h^{-1} for the catalytic system using the more rigid ephedrine and $[RuCl_2(benzene)]_2$ ligands.[25] Also, our catalysts are an order of magnitude less active than the described *cis*-$[RuCl_2(P\textit{i}\text{-}Pr_3)(\kappa^3\text{-}N,N,N\text{-Ph-pybox})]$[8] with a TOF of 9000 h^{-1} (after 3 min and 97% conversion). The known ligand (1*R*,2*R*)-*N*-tosyl-1,2-diaminocyclohexane **2** (Fig. 1)[26] was subjected to the same conditions (entries 16 and 17) and exhibited poor reactivity (TOF_{50} 2 h^{-1}, entry 16), but gave a strong increase in enantioselectivity after prolonged reaction times.

The activities did not correlate with the electronic or steric properties of the ligands. Ligand **1e** gave the best enantioselectivitiy (82% ee) and was therefore chosen for further investigations.

2.2. Thermal activation of the catalyst

Treating our ligands and $[IrCp^*Cl(\mu\text{-}H)]_2$ in *i*-PrOH at reflux prior to reaction for at least 10 min had a positive effect on the activity and enantioselectivity of the in situ

formed catalyst. To investigate this observation, we first examined the behavior of $[IrCp^*Cl(\mu\text{-}H)]_2$ in *i*-PrOH without any ligand. At room temperature, $[IrCp^*Cl(\mu\text{-}H)]_2$ dissolved very slowly and only in traces. The color of the resulting blue suspension turned to purple after warming to 40 °C, while heating the mixture at reflux for more than 10 min gave a bright yellow solution. Mass spectrometry (ESI) gave a single signal at *m*/*z* 657 corresponding to $\{[IrCp^*]_2(\mu\text{-}H)_3\}Cl$, which was previously prepared by hydrogenation of $[IrCp^*Cl_2]_2$.[27] The formation of this complex was also confirmed by ^1H NMR experiments. $[IrCp^*Cl(\mu\text{-}H)]_2$ and *i*-PrOH-d_6 were placed in an NMR tube and the process of dissolution monitored. The chemical shift at −15.46 ppm corresponded exactly with the control experiment using $\{[IrCp^*]_2(\mu\text{-}H)_3\}PF_6$ in *i*-PrOH-d_6 and was almost identical with the signal at −15.33 ppm in $CDCl_3$.[28]

Immediately after the addition of 2 equiv of *i*-PrOK to a similar activated solution, we could observe new signals in the mass spectrum. The strongest of them had *m*/*z* 463 and corresponded to $[IrCp^*_2]^+$, which was confirmed by the synthesis of $[IrCp^*_2]BF_4$.[29] $[IrCp^*_2]BF_4$ indeed acted as an Ir-source and showed steady, but only with decent activity (Table 1, entry 6).

We concluded that $[IrCp^*Cl(\mu\text{-}H)]_2$ was hydrogenated to $\{[IrCp^*]_2(\mu\text{-}H)_3\}^+$ with oxidation of *i*-PrOH to acetone and formation of 0.5 molecule HCl per Ir (Scheme 1). Therefore, the formation of the chiral catalyst must begin with the breakdown of $\{[IrCp^*]_2(\mu\text{-}H)_3\}^+$.

2.3. Stability of the catalyst

We expected the presence of a very active catalyst at the beginning of the reaction with a short lifetime and some catalytically less active species, which later led to slow conversion over several hours. The stability of {(*P*)-**1e**/$[IrCp^*Cl(\mu\text{-}H)]_2$} was determined by kinetic experiments using 2 equiv of *i*-PrOK (experimental data available). The older the catalyst, the slower the initial rate of the reduction of acetophenone. The decay of the catalyst followed a first order rate equation and the catalytically active species present at the very beginning, had a half-life period of 11 min. The same experiment using different amounts of *i*-PrOK has so far not been accomplished.

2.4. Base dependent activities and enantioselectivities

The results of a series of experiments with ligand **1e** using different amounts of *i*-PrOK are shown in Figure 2. From 0.2 to 0.6 equiv, the conversion increased from 6% to 33% after 30 min. More base seemed to inhibit the reaction between 0.6 and 1.2 equiv, however almost full activity was observed above 1.4 equiv. Increasing the amount of base to 10 equiv gave no further increase in activity.

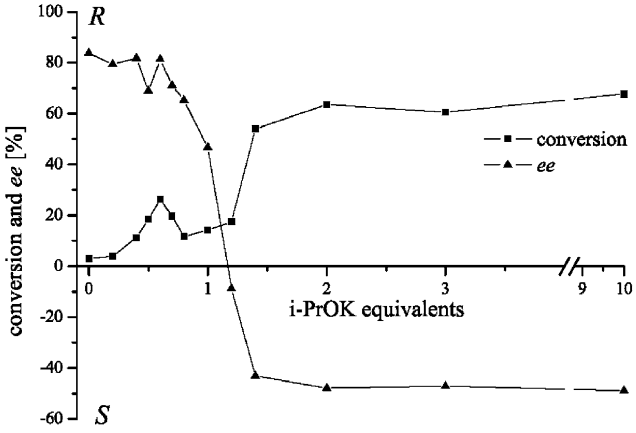


Figure 2. Base dependent conversions and enantioselectivities in the transfer hydrogenation of acetophenone (100 mM)/(*P*)-**1e**/$[IrCp^*Cl(\mu\text{-}H)]_2$/*i*-PrOK = 100:1.0:0.5:0.1–10. 23 °C, data recorded after 30 min.

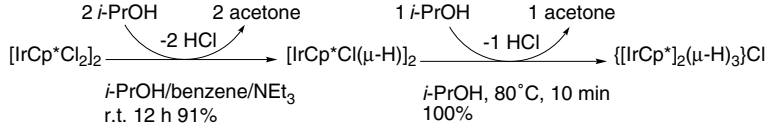
By altering the amount of base, we were able to influence not only the activity, but also the enantioselectivity of the reaction. With a small increase from 0.6 to 1.4 equiv, the ee changed from 82% (*R*) to 49% (*S*). This very unusual finding was observed with all ligands **1a**–**e**, but not with ligand **2**.

2.5. Discussion about the possible origin of inversion

During the thermal activation, which facilitates the hydrogenation of $[IrCp^*Cl(\mu\text{-}H)]_2$ to $\{[IrCp^*]_2(\mu\text{-}H)_3\}Cl$, the HCl formed protonates 50% of the amino groups of the ligand (Scheme 1). The remaining amino groups keep the mixture buffered at a basic pH and allow the reaction to slowly proceed even if no base is added.

The first 0.5 equiv *i*-PrOK added to the mixture only regenerated the ligand in its neutral form. Up to this point a catalytic active species is present, which leads predominantly to the (*R*)-enantiomer. Most of the coordination sites of the ligand are blocked and the iridium very likely coordinates in a monodentate fashion rather than forming a stable bidentate chelate.

If greater than 0.5 equiv of *i*-PrOK was added, the excess deprotonated the sulfonamide (pK_a about 14). The ligand would then reach its full coordination capacity and readily bind to the metal to form a species, which leads predominantly to the (*S*)-enantiomer. Furthermore, the ligand acts as a buffer. When we used 1 equiv



Scheme 1. Hydrogenation of $[IrCp^*Cl_2]_2$ and $[IrCp^*Cl(\mu\text{-}H)]_2$ with *i*-PrOH under formation of HCl and acetone.

of (*P*)-**1e** and 2 equiv of *i*-PrOK, we obtained the (*S*)-configured product in 49% ee after 30 min. Using 4 equiv of the ligand gave the (*R*)-configured product in 79% ee. The excess of ligand acted as a weak acid (sulfonamide) and neutralized the *i*-PrOK. As a speculation, *i*-PrOK could in an analogous fashion to *t*-BuOK deprotonate $\{[Ir(III)Cp^*]_2(\mu\text{-}H)_3\}^+$ leading to $[Ir(II)Cp^*(\mu\text{-}H)_2]_2$.[28]

We performed ^1H NMR experiments focusing on hydridic Ir-complexes. Unfortunately we were not able to assign any of the observed signals to a catalyst. This could mean that the catalyst was present in a concentration not detectable by NMR spectroscopy or the iridium in the catalyst did not bear a hydride. Analysis of the reaction mixtures at different stages with mass spectrometry (ESI) did not reveal a signal assignable to an Ir-complex containing our ligand.

3. Conclusions

We found a reasonably active catalytic system with $[IrCp^*Cl(\mu\text{-}H)]_2$ and different flexible axially chiral monosulfonated diamines for the transfer hydrogenation of acetophenone in *i*-PrOH. The stereochemical outcome could be altered by controlling the amount of base in a very narrow range. We assumed that the availability of the binding sites at different pH levels may play a crucial role in this change of mechanism. However, the structures of the two catalysts at low and high base concentrations remain to be determined.

Acknowledgments

This work was funded by the Canton Zurich. We also thank our MS- and NMR-facilities for support.

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