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Asymmetric Transfer Hydrogenation

Iridium Diamine Catalyst for the Asymmetric Transfer Hydrogenation of Ketones**

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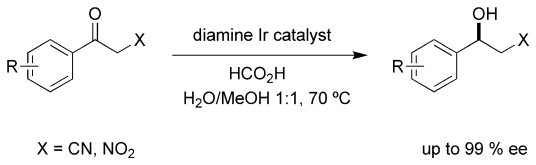
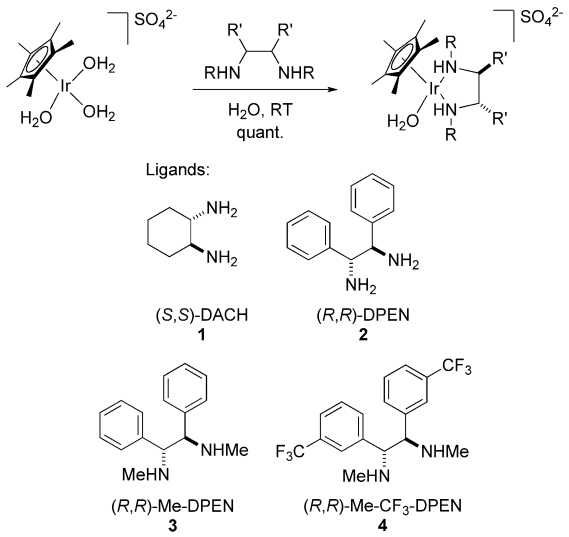
Catalytic asymmetric transfer hydrogenation (ATH) of ketones has emerged as an attractive alternative to the use of hydrogen for the preparation of optically active secondary alcohols.[1] The majority of the research carried out in this area has relied on Ru^{II} catalysts bearing optically active phosphines and amino/sulfonamides.[1] Among the most widely employed catalytic systems is that of Noyori et al., namely the Ru^{II}–TsDPEN catalyst (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine), which displays broad substrate scope and provides optically active alcohols in high enantiomeric purity.[2] Herein we report the synthesis, isolation, and application of a new chiral aqua iridium(III) complex for the ATH of aromatic α-cyano and α-nitro ketones, substrates whose reduction has not yet been widely studied (Scheme 1).[3a–c] The catalytic system described is based on commercially available, optically active diamines, which are simplified ligand alternatives to the commonly used monosulfonylated diamines.



Scheme 1. ATH with iridium diamine complexes.

Ogo, Fukuzumi, and co-workers have documented the ability of $[Cp^*Ir(bpy)(H_2O)]SO_4$ (bpy = 2,2′-bypyridine, $Cp^* = C_5Me_5$) to effectively reduce ketones through the action of formate ions in a pH-dependent process.[3,4] Recently, the Xiao[5] and Deng[6] groups have shown that chiral iridium(III) catalysts are an attractive alternative to the use of ruthenium(II) systems in the ATH processes of ketones in water. These catalytic systems are generated by allowing $[\{Cp^*IrCl_2\}_2]$ to react with the monosulfonylated diamine CsDPEN (CsDPEN = *N*-(camphorsulfonyl)-1,2-diphenylethylenediamine) and TsDPEN. However, the number of reports involving iridium published to date remains scarce when compared to those using ruthenium(II)-based systems.[7] Moreover, none of these employ simple secondary C_2-symmetric diamines as chiral ligands.[8–11] Bearing in mind the complex developed by Ogo, Fukuzumi, and co-workers, we decided to explore the use of chiral aqua iridium complexes in ATH.

The chiral aqua iridium(III) complexes $[Cp^*Ir(ligand)(H_2O)]SO_4$ were easily prepared by mixing $[Cp^*Ir(H_2O)_3]SO_4$ with a collection of chiral diamines in water at room temperature (Scheme 2). These complexes were isolated as



Scheme 2. Synthesis of iridium(III) complexes.

air- and moisture-stable solids that could be used directly in the ATH reaction. Screening of the various Ir complexes was carried out for the reduction of 2-cyanoacetophenone with formate ion using a 1:1 water/methanol solvent mixture in an open reaction flask. As shown in Table 1 the reaction with 0.5 mol% of the corresponding complex and 5 equivalents of sodium formate at 70°C led to the expected 2-hydroxynitrile with variable yields and *ee* values (Table 1, entries 1–5). The complexes with ligands **1** and **2** gave low enantiomeric excesses (47% and 43%, respectively; Table 1, entries 2 and 3); however, the reaction catalyzed by the complex $[Cp^*Ir(\mathbf{3})(H_2O)]SO_4$ yielded the corresponding alcohol in 83% *ee* (Table 1, entry 4). At this point, further significant improvement in the enantioselectivity was achieved by introduction of a trifluoromethyl group into the phenyl rings of the diamine (**4**). Using the complex derived from this ligand, we obtained 2-hydroxynitrile in 95% *ee* (Table 1, entry 5). Finally, the use

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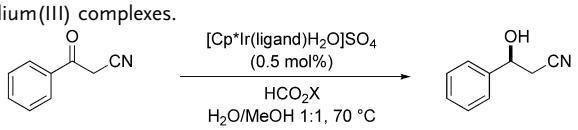
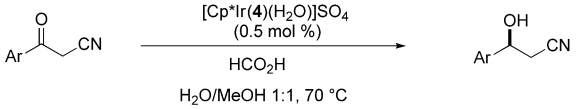
Table 1: ATH reaction of 2-cyanoacetophenone catalyzed by chiral iridium(III) complexes.



Entry[a]	Ligand	HCO_2X	Yield [%][b]	*ee* [%]
1	bpy	HCO_2Na	87	–
2	**1**	HCO_2Na	90	47
3	**2**	HCO_2Na	79	43
4	**3**	HCO_2Na	63	83
5	**4**	HCO_2Na	84	95
6	**4**	HCO_2H	99	95

[a] Reactions were carried out at 70 °C using 1 mmol of ketone in 5 mL of a 1:1 mixture of water/methanol with 0.5 mol% of [Cp*Ir(ligand)H_2O]SO_4. [b] Yield and *ee* were determined by GC.

Table 2: ATH reaction of 2-cyanoacetophenones with [Cp*Ir(**4**)-(H_2O)]SO_4.



Entry[a]	Ar	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	C_6H_5	12	96	95
2	*o*-MeC_6H_4	24	92	99
3	*p*-MeC_6H_4	18	93	92
4	*o*-$MeOC_6H_4$	24	90	99
5	*m*-$MeOC_6H_4$	15	91	97
6	*p*-$MeOC_6H_4$	20	90	90
7	*o*-IC_6H_4	44	45	99
8	*p*-BrC_6H_4	18	87	90
9	*p*-FC_6H_4	18	85	87
10	*m*-$NO_2C_6H_4$	12	96	87
11	2-naphthyl	15	88	95
12	1-thienyl	20	92	73

[a] Reactions were carried out at 70 °C using 1 mmol of ketone in 5 mL of a 1:1 mixture of water/methanol with 0.5 mol% of catalyst and 5 equivalents of HCO_2H. [b] Yield of isolated product. [c] Determined by GC or HPLC analysis with a chiral stationary phase. [d] Configuration of the products were all determined to be *S* as shown by the optical rotation values.

of formic acid instead of sodium formate resulted in improved catalyst efficiency (> 99% conversion) without detriment to the enantioselectivity (Table 1, entry 6). The fact that the reaction may be conducted at pH 2 (formic acid) as well as at pH 5.5 (sodium formate) without affecting the selectivity renders it a highly flexible process. This is remarkable as it is in contrast with the reactivity shown for the Ru^{II}–TsDPEN system, where it has been noted that conducting the reaction in acidic media leads to a decrease in enantioselectivity.[4c]

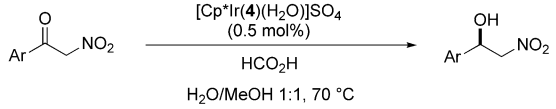
The initial results obtained with [Cp*Ir(**4**)(H_2O)]SO_4 prompted us to study this system further with a diverse range of substituted 2-cyanoacetophenones. We chose as standard conditions those that gave the best conversion (Table 1, entry 6), wherein the starting 2-cyanoacetophenone was heated at 70 °C in the presence of 0.5 mol% of [Cp*Ir(**4**)-(H_2O)]SO_4 and 5 equivalents of HCO_2H using a 1:1 mixture of water/methanol as solvent. The results obtained are shown in Table 2.

In general, the majority of the substrates tested were reduced under the standard conditions, affording the β-hydroxynitriles in good yield and enantiomeric excess (up to 99% *ee*). Both electron-donating and electron-withdrawing substituents were well tolerated in the substrates examined in the ATH reaction; indeed the substitution pattern had no significant influence on the reaction time needed to achieve conversions. However, those systems with electron-withdrawing substituents yielded the reduction products with slightly lower selectivity (Table 2, entries 8–10). It is well worth noting that *ortho*-substituted arenes furnished products displaying higher enantiomeric excess than those obtained from the corresponding *meta* and *para* isomers (Table 2, entries 2–6). Thus, in the case of methoxy-substituted 2-cyanoacetophenones (Table 2, entries 4–6), the *ortho* regioisomer was reduced with 99% *ee*, and the *para* isomer delivered the alcohol in only 90% *ee*. A similar trend was found also for the corresponding methyl-substituted 2-cyanoacetophenones (Table 2, entries 2 and 3, 99% *ee* (*ortho*) versus 92% *ee* (*para*)). The beneficial "*ortho* effect" was also confirmed in the case of acetophenones bearing electron-withdrawing substituents such as iodine (99% *ee*). These results are in contrast with the widely reported effect found in the ATH reaction of substituted acetophenones, where *ortho*-substituted systems lead to products with lower enantiomeric excess. For example, ATH of 1-(*p*-methoxyphenyl)ethanone catalyzed by Ir–CsDPEN yielded the corresponding alcohol with 97% *ee*, while the enantiomeric excess for the *ortho* isomer was 85% *ee*.[5a] The same effect was also observed when the system Ru–TsCYDN (TsCYDN = *N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine) was used as the catalyst, and 1-*p*-tolylethanone was reduced with 92% *ee* while 80% *ee* was obtained for 1-*o*-tolylethanone.[5b]

The reductions of 2-nitroacetophenones were also examined with the catalytic system described herein, [Cp*Ir(**4**)-(H_2O)]SO_4 and HCO_2H, and the results are summarized in Table 3. When the reaction was examined using the standard conditions described above for the reduction of 2-cyanoacetophenones, the corresponding 2-nitroalcohols were obtained with good enantiomeric excesses (up to 98% *ee*) and moderate to good yields (Table 3, entries 1–5). The reduction of *meta*-bromo-2-nitroacetophenone was better achieved with a slight modification of the standard reaction conditions. Thus, when the solvent was changed from water/methanol to a 1:1 mixture of water/formic acid, which caused a drop in the pH from 5.5 to 2.0, both the reaction time and the yield were improved (Table 3, entry 5 versus entry 6), without a significant change in the enantioselectivity. These latter conditions were successfully applied to the reduction of *meta*-chloro-2-nitroacetophenone (Table 3, entry 7). The heteroaromatic system 2-nitro-1-(thiophen-2-yl)ethanone was also reduced using these modified conditions with moderate yield and enantioselectivity (Table 3, entry 9).

In summary, we have developed a new, simple, and highly efficient chiral aqua iridium(III) complex for ATH. This catalytic system has shown high reactivity, leading to excellent enantioselectivities (up to 99% *ee*) for various aromatic α-cyano and α-nitro ketones. An additional advantage of this

Table 3: ATH reaction of 2-cyanoacetophenones with [Cp*Ir(**4**)-(H_2O)]SO_4.



Entry[a,b]	Ar	*t* [h]	Yield [%][b]	*ee* [%][d]
1[a]	C_6H_5	5	85	95
2[a]	*o*-MeC_6H_4	18	51	99
3[a]	*p*-*t*BuC_6H_4	8	77	92
4[a]	*o*-$MeOC_6H_4$	12	75	98
5[a]	*m*-BrC_6H_4	15	35	94
6[b]	*m*-BrC_6H_4	3	78	93
7[b]	*m*-ClC_6H_4	2	81	92
8[a]	2-naphthyl	10	78	93
9[b]	2-thienyl	9	50	76

[a] Reactions were carried out at 70 °C using 1 mmol ketone in 5 mL of a 1:1 mixture of water/methanol with 0.5 mol% of catalyst and 5 equivalents of HCO_2H. [b] Reactions were carried out at 70 °C using 1 mmol of ketone in 5 mL of a 1:1 mixture of water/HCO_2H with 0.5 mol% of catalyst. [c] Yield of isolated product. [d] Determined by HPLC analysis with a chiral stationary phase. [e] Configuration of the products were all determined to be *R* as shown by the optical rotation values.

catalyst is the "*ortho* effect" observed, which leads to *ortho*-substituted aromatic alcohols with high enantioselectivity. Of particular importance is the fact that the diamines can be used as the chiral ligands without conversion to the corresponding monosulfonylated diamines. This leads to a significant simplication of the ligand and its synthesis. Moreover, it opens up new opportunities for ligand design which have otherwise focused on monosulfonamides of diamines. Further exploration of these iridium(III) catalytic systems is underway and results will be reported in due course.

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