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Asymmetric hydrogenation of ketones using Ir(III) complexes of *N*-alkyl-*N*′-tosyl-1,2-ethanediamine ligands

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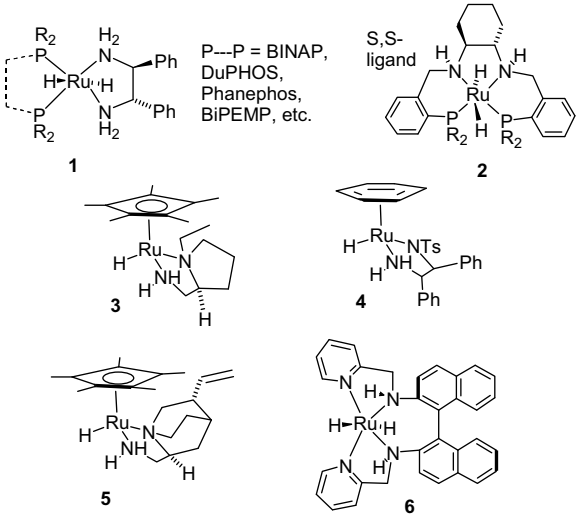
ABSTRACT

The combination of an enantiomerically pure N′-alkylated derivative of *N*-4-toluenesulfonyl-1,2-diphenylethane-1,2-diamine (TsDPEN) with iridium trichloride results in the formation of a catalyst with high selectivity for ketone hydrogenation. Products with enantiomeric excesses of up to 84% were formed. The best results were obtained using a ligand with an *n*-alkyl chain and *ortho*-substituted acetophenone derivatives and other hindered derivatives.

In asymmetric hydrogenation reactions of C=C, C=O and C=N bonds using hydrogen gas, the most commonly used catalysts are those formed between one or more monodentate or bidentate phosphorus-donor ligands and a transition metal.[1] The addition of a suitable nitrogen-containing donor ligand such as a diamine to a diphosphine/metal complex is known to furnish modified catalysts **1** which are capable of the asymmetric hydrogenation of C=O double bonds in excellent enantioselectivity and high activity.[2] There are also examples of complexes such as **2** which contain a mixed phosphorus/nitrogen donor ligand.[3,4]

Complexes of amine-based ligands provide a potential advantage over phosphorus-based ligands since they are less prone to aerial oxidation. Ikariya has reported the use of catalyst **3** which contains a tertiary amine/primary amine combination ligand with Ru(II), in asymmetric ketone hydrogenation.[5] Noyori, and others, have reported that complex **4**,[6] which is more commonly associated with asymmetric transfer hydrogenation (ATH),[6d–g] becomes a hydrogenation catalyst when used in methanol rather than isopropanol.[6a–c] The rhodium(III) and iridium(III) derivatives of this complex, which feature a pentamethylcyclopentadiene group in place of the η^6-arene, have also been used successfully in ketone reduction by hydrogen[6d] and in ATH.[6e,f] Andersson et al. have reported the development of an efficient catalyst of structure **5**.[7] Thomas et al. have demonstrated that a diamine/Rh(I) catalyst can be supported on silica and acts as an efficient promoter of the asymmetric reduction of α-amino ketones.[8] Kitamura et al. demonstrated the successful use of the tetradentate nitrogen-donor ligand complex **6** as a Ru(II) based asymmetric ketone hydrogenation catalyst.[9]



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The proposed reduction transition states through which each of the above catalysts transfer hydrogen to a ketone are believed to involve a six-centre hydrogen-transfer process (Fig. 1).[10] This mechanism is facilitated by a hydrogen on the nitrogen atom in

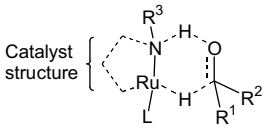

Figure 1. Six-centre mechanism of hydrogen transfer by catalysts **1**–**6**.

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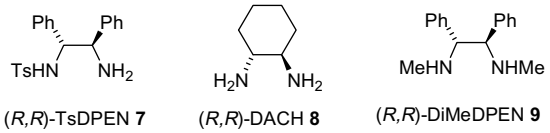
each case, which forms a hydrogen bond to the oxygen atom of the ketone substrate. The speculated mechanism is supported by a number of mechanistic and kinetic studies on this class of catalyst.[10]

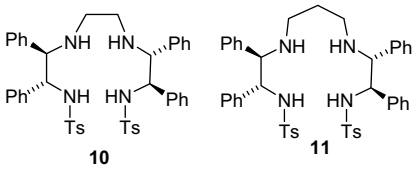
A number of Ir-based diamine complexes have been reported for ketone reduction.[6d–g,11–21] The combination of (*R,R*)-*N*-tosyl-1,2-diphenylethylene-1,2-diamine **7** (*R,R*-TsDPEN) and $[Ir(COD)Cl]_2$ in MeOH/toluene was reported to reduce a β-keto ester under 10 bar hydrogen in 36% yield and 11% ee (*S*).[11] The related ATH of acetophenone using (*R,R*)-TsDPEN **7**/$[Ir(COD)Cl]_2$ gave the corresponding product in up to 87% yield and 92% ee (*S*).



(*R,R*)-TsDPEN **7** (*R,R*)-DACH **8** (*R,R*)-DiMeDPEN **9**

A complex of (*R,R*)-1,2-diaminocyclohexane **8** (*R,R*-DACH) and *N,N′*-dimethyl-1,2-diphenylethylene-1,2-diamine **9** (DiMeDPEN) with $[Ir(COD)_2]BF_4$ has been used for hydrogenation of α-keto esters.[15a] The use of 5 mol % catalyst gave products in 100% yield and 72% ee (*R*) with DiMeDPEN **9** and 31% ee (*R*) with (*R,R*)-DACH **8**. Hydrophilic *N,N′*-dimethyl DPEN diamines have been used with $[Ir(COD)_2]BF_4$ complexes and gave products in up to 80% ee in hydrogenations of α-keto esters and 68% ee for acetophenone.[15b,c] Water soluble *N,N′*-dimethyl DPEN complexes of Ir(I) salts gave better results than Ru or Rh and 84% ee for the reduction of PhCO*t*-Bu.[16]

We wished to examine further combinations of tetradentate, amine-based, ligands with transition metals. In a preliminary screen, we used ligands **10** and **11** with a series of Ru(II), Ru(III), Rh(III) and Ir(III) complexes (Table 1) for the reduction of acetophenone **12**.[21] Without ligands, a mixture of reduction products **13–15** were formed, including those of aromatic ring reduction. In the case of $RuCl_3$, full reduction to racemic 1-cyclohexylethanol represented the major outcome. In the case of $RuCl_2(DMSO)_4$, the reduction product was formed incompletely and in moderate ee. Whilst the $RhCl_3$ complex also gave the C=O reduction product as the major product, it was formed in low ee. However, this represented a major change from the over-reduced product formed in the absence of ligand. The most interesting result, however, was obtained using $IrCl_3$ as the metal, since 1-phenylethanol **15** was formed as the exclusive product (100% conversion) in 25% and 37% ee, respectively. The iridium(III) results led us to examine further ligand/metal combinations.



To establish whether or not the tetradentate amine is required, we employed (*R,R*)-*N*-benzyl-TsDPEN **16** in the reduction. The results paralleled those obtained with each of the tetradentate ligands, and acetophenone was reduced in 100% conversion after 48 h in 41% ee (*S*).

The results clearly indicate that an N-alkylated derivative of (*R,R*)-TsDPEN, in combination with $IrCl_3$, forms a competent catalyst for the selective reduction of ketones. We suspected that the tetradentate ligands may be operating as two independent bidentate ligands. Indirect evidence that this was the case was obtained by the use of two equivalents of $IrCl_3$ with **10**, which resulted in an increase of the product ee to 43% without loss of activity.

In view of the observed ligand effect using Ir(III), we examined the effect of the base concentration on the reaction, having so far used an initial loading of 30 mol %. Using two new ligands, the *N*-ethyl **17** and *N*-3-phenylpropyl TsDPEN **18,** respectively, the ees of reduction of acetophenone peaked at 59% for both (Table 2). At very low loadings of base and particularly less than 10 mol %, the ee dropped to very low levels. These results suggest that an equilibrium may be operating in which a 'reservoir' of active catalyst is accumulated by the excess base.[22]

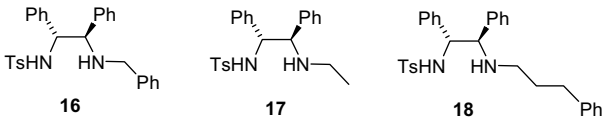
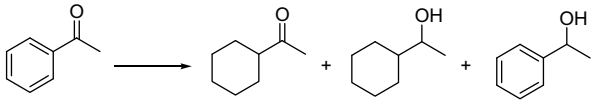


Table 1
Hydrogenation of acetophenone **12** to products **13–15**[a]



Entry	Metal[b]	Ligand	Conv (%)	**13** (%)	**14** (%)	**15** (%)	ee (**15**) (%)
1	Ru(II)	None	0	0	0	0	—
2	Ru(III)	None	100	18	31	51	—
3	Rh(III)	None	100	0	100	0	—
4	Ir(III)	None	98	39	0	59	—
5	Ru(II)	**10**	36[c]	0	0	36	12 (*R*)
6	Ru(II)	**11**	72	0	0	72	12 (*R*)
7	Ru(II)	**16**	81	0	0	81	32 (*R*)
8	Ru(III)	**10**	100[c]	0	95	5	0
9	Ru(III)	**11**	100	0	77	23	0
10	Ru(III)	**16**	100	0	98	2	0
11	Rh(III)	**10**	99[c]	1	11	88	12 (*S*)
12	Rh(III)	**11**	100	0	5	95	12 (*S*)
13	Rh(III)	**16**	100	0	21	79	5 (*S*)
14	Ir(III)	**10**	100	0	0	100	25 (*S*)
15	Ir(III)[d]	**10**	100	0	0	100	43 (*S*)
16	Ir(III)	**11**	100	0	0	100	37 (*S*)
17	Ir(III)	**16**	100	0	0	100	41 (*S*)

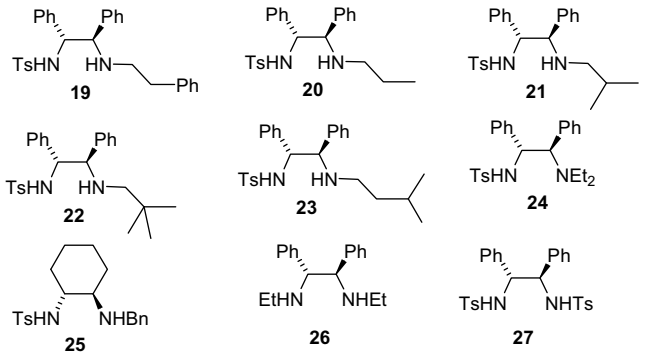
[a] Conditions: 1 M acetophenone in methanol (1 mL); 1% $IrCl_3$/ligand (1:1), 50 bar hydrogen, 30–50 mol % base, 40 °C, 48 h unless otherwise stated.
[b] Ru(II); $RuCl_2(DMSO)_4$, Ru(III); $RuCl_3$, Rh(III); $RhCl_3$, Ir(III); $IrCl_3$.
[c] 24 h.
[d] 2 equiv ligand used.

Table 2
Effect of base on the enantioselectivity of ketone reduction[a]

Ligand	**17**		**18**	
NaOH/catalyst	Conv. (%)	Ee (%)	Conv. (%)	ee (%)
1	100[b] (85)	0	100[b] (80)	0
2	100[b] (71)	0	100[b] (82)	1 (*S*)
3	100[b] (80)	1 (*S*)	100[b] (84)	1 (*S*)
5	96	32 (*S*)	96	32 (*S*)
10	100	37 (*S*)	100	39 (*S*)
20	100	53 (*S*)	100	48 (*S*)
30	100	56 (*S*)	100	59 (*S*)
40	100	59 (*S*)	100	56 (*S*)
50	100	55 (*S*)	100	50 (*S*)
60	100	55 (*S*)	100	50 (*S*)

[a] Reduction of acetophenone to 1-phenylethanol using $IrCl_3$ and catalysts **17** and **18**. 50 bar hydrogen , 1 mol % catalyst, MeOH, $IrCl_3$:ligand 1:1, 40 °C, 24 h.
[b] Products of reduction of the aromatic ring also formed, isolated yields of alcohol are given in brackets.

A series of further ligand derivatives **19**–**27** were tested in acetophenone reduction (Table 3). Conversions were typically excellent and ees were within the range of 36–60% (in all cases, the *R,R*-ligand led to product of *S* configuration), although the best results were obtained using sterically uncongested *N*-alkyl groups. For example, the product ee increased from 2-phenylethyl **19** through 3-phenylpropyl **18** to *N*-benzyl **16**, and the best results were obtained using a ligand with an *N*-propyl group, that is, **20**. A ligand containing a tertiary amine group **24**[23] was less active (entry 9). (*R,R*)-TsDPEN **7** itself gave a product of just 18% ee and with a reversed sense of induction relative to the alkylated derivatives.[23b] *N,N′*-diethylDPEN **26**[23d] gave a product of 55% ee (*S*) and *N,N′*-ditosylated DPEN ligand **27**,[24] a product of 34% ee (*S*). *N,N′*-dialkylated DPENs have been reported in asymmetric ketone hydrogenation in the form of Ir(III) complexes.[14–16] However, the best results were achieved using the combined tosylated/alkylated ligands, a novel combination. Although the high regioselectivity of the diamine/Ir(III) combination is maintained in all examples, N-substituents are required for optimal enantioselectivity; in combination with $IrCl_3$, (*R,R*)-DPEN itself gave a product of just 29% ee (*S*).



The effect of pressure on the reaction was examined using the *N*-benzyl **16** and *N*-3-phenylpropyl **18** ligands. We had previously run the reactions at 50 bar pressure, however, this could be reduced to 30 bar without significant loss of ee. At 10 bar pressure, however, the enantioselectivities dropped significantly. The reduction of an extended series of aromatic ketones (Fig. 2) was undertaken using a selection of some of the more effective ligands (Table 4). Ketones **28**–**33** represent two series in which either a methyl group (**28**–**30**) or a methoxy group (**31**–**33**) is present in a different aromatic position. In every case, ligand **20** gave the best result, although it was often only marginally better than the next best ligand. Most interesting was the observation that the *ortho*-substituted substrate gave a product of as good, if not the best, enantioselectivity compared to the *meta* and *para* substituted substrates. *Ortho*-substituted substrates can often be difficult to reduce in high ee, although a number of examples of efficient hydrogenation catalysts have been reported.[2a,25]

A systematic series of ketones **34**–**37** permitted the investigation of the effect of the size of the alkyl group adjacent to the aryl in each substrate. Again the results were surprising because the most hindered substrate, that is, **37**, was reduced with the highest enantioselectivity, and the results revealed an increasing ee as the group in this position became larger. Hindered ketones of this type are regarded as challenging substrates and in this respect, this method represents a useful alternative to other established methods.[25] An *N,N′*-dimethylated DPEN derivative has been reported to furnish a product of 72% ee upon hydrogenation of **37** with an Ir(I) salt as the metal source.[16]

In addition to the dimethyl substituted ketone **38**, a small series of halogen and methoxy substituted ketones **39**–**42** were subjected to enantioselective reduction using the Ir(III)/diamine method and again the results revealed that the *ortho*-substituted substrates, including electron-rich substrates such as **42**, were compatible with this catalyst system. Trifluoromethyl substitution, as in **43** and **44**, did not hinder the reductions. In the case of naphthyl substituted substrates **45** and **46**, the apparently hindered substrate **45** was reduced with the highest enantioselectivity. 1-Tetralone **47** was reduced in higher ee than 2-tetralone **48**. Ketones containing a heteroaromatic ring in place of the aromatic ring (i.e., **49**–**52**) were compatible with the reduction conditions, however, they were all reduced in low ee or with no detectable enantioselectivity (<7%). The catalyst system also seems to be specific for substrates containing an aromatic ring—acetylcyclohexane **53** was reduced in only 16% ee (*S*).

A brief investigation was conducted into the effect of solvent on the reduction reactions. The use of ethanol or isopropanol gave inferior results compared to methanol, in terms of conversion and ee. The absence of competing ATH was confirmed by attempting the reduction of acetophenone in the absence of an atmosphere of hydrogen; no reduction was observed after 24 h.

Table 3
Asymmetric hydrogenation of acetophenone **12** using $IrCl_3$ with diamine ligands[a]

Entry	Ligand	Conv. (%)	ee (%)
1	**16**	100	59 (*S*)
2	**17**	100	57 (*S*)
3	**18**	100	56 (*S*)
4	**19**	100	51 (*S*)
5	**20**	100	60 (*S*)
6	**21**	100	54 (*S*)
7	**22**	100	36 (*S*)
8	**23**	100	50 (*S*)
9	**24**	59	30 (*S*)
10	**7** (TsDPEN)	100	18 (*R*)
11	**25**	99	45 (*S*)
12	**26**	100	55 (*S*)
13	**27**	100	34 (*S*)

[a] Conditions: 1 M acetophenone in methanol (1 mL); 1% catalyst, 50 bar hydrogen, NaOH:catalyst = 30:1, 40 °C, 24 h.

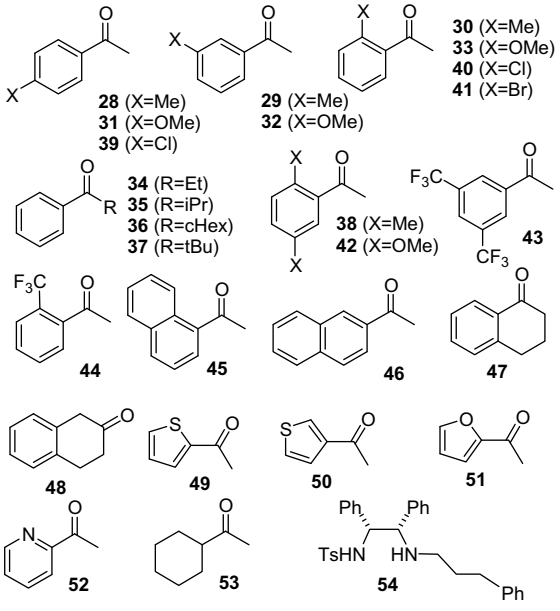


Figure 2. Ketones used in extended reduction studies (Table 4).

Table 4
Reductions of ketones **28**–**48** using $IrCl_3$/chiral diamines[a]

Entry	Ketone	Ligand	N-R	Conv (%)	ee (%)
1	**28**	**18**	$(CH_2)_3Ph$	100	63 (*S*)
2	**28**	**19**	$(CH_2)_2Ph$	100	63 (*S*)
3	**28**	**20**	*n*-Pr	100	66 (*S*)
4	**29**	**18**	$(CH_2)_3Ph$	100	61 (*S*)
5	**29**	**20**	*n*-Pr	100	68 (*S*)
6	**30**	**18**	$(CH_2)_3Ph$	100	83 (*S*)
7	**30**	**20**	*n*-Pr	100	84 (*S*)
8	**31**	**18**	$(CH_2)_3Ph$	92	64 (*S*)
9	**31**	**20**	*n*-Pr	98	72 (*S*)
10	**32**	**18**	$(CH_2)_3Ph$	100	58 (*S*)
11	**32**	**20**	*n*-Pr	99	59 (*S*)
12	**33**	**17**	Et	100	69 (*S*)
13	**33**	**18**	$(CH_2)_3Ph$	100	68 (*S*)
14	**33**	**19**	$(CH_2)_2Ph$	100	69 (*S*)
15	**33**	**20**	*n*-Pr	100	71 (*S*)
16	**34**	**17**	Et	100	60 (*S*)
17	**34**	**20**	*n*-Pr	100	66 (*S*)
18	**35**	**20**	*n*-Pr	97	69 (*S*)
19	**36**	**20**	*n*-Pr	73	73 (*S*)
20	**37**	**17**	Et	100	68 (*S*)
21	**37**	**20**	*n*-Pr	100	73 (*S*)
22	**38**	**20**	*n*-Pr	100	83 (*S*)
23	**39**	**16**	CH_2Ph	100	30 (*S*)
24	**39**	**18**	$(CH_2)_3Ph$	100	59 (*S*)
25	**40**	**20**	*n*-Pr	100	66 (*S*)
26	**41**	**20**	*n*-Pr	100	53 (*S*)
27	**42**	**20**	*n*-Pr	100	76 (*S*)
28	**43**	**20**	*n*-Pr	100	27 (*S*)
29	**44**	**20**	*n*-Pr	100	74 (*S*)
30	**45**	**17**	Et	100	54 (*S*)
31	**45**	**20**	*n*-Pr	100	66 (*S*)
32	**46**	**17**	Et	100	40 (*S*)
33	**46**	**20**	*n*-Pr	100	51 (*S*)
34	**47**	**17**	Et	94	64 (*S*)
35	**47**	**20**	*n*-Pr	100	76 (*S*)
36	**48**	**20**	*n*-Pr	100	17 (*S*)

[a] Conditions: 1 mol % catalyst (ligand:Ir(III) 1:1), NaOH: catalyst = 30:1, [ketone] = 1 M, MeOH, 50 bar hydrogen, 40 °C, 24 h.

The use of the *trans*-diamine ligand is also important; the cis-derivative of **18**, that is, ligand **54**, gave reduction of acetophenone **12** in 73% yield and just 7% ee and reduction of ketone **29** in only 24% yield and 2% ee.

In conclusion, we have demonstrated that the combination of $Ir(III)Cl_3$ with an alkylated TsDPEN derivative results in the formation of a competent catalyst for asymmetric ketone hydrogenation. In the best cases and for certain substrates (e.g., **30**, **37**, **38**), the levels of enantiomeric excess obtained are comparable with those obtained using more complex catalysts. The catalysts benefit from simplicity of preparation; the ligands are typically prepared in one step by reductive alkylation of commercially-available TsDPEN (see Supplementary data). Additionally, the most basic of precious metal salts is required for the preparation of the catalysts. Our observations suggest that a 1:1 diamine:Ir(III) complex is formed, however, we are continuing to work towards gaining an understanding of the mechanism and the use of further catalyst derivatives.

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Supplementary data

General experimental details, ligands and alcohols not described above, and ^1H and ^{13}C NMR of all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.101.

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